RHEUMATIC FEVER

Epidemiology and Prevention

THE PROCEEDINGS OF A SEMINAR
HELD AT THE
INTERNATIONAL CHILDREN'S CENTRE
PARIS, 25-27 SEPTEMBER 1956

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PREFACE

Shortly after the French edition of this monograph on the Epidemiology and Prevention of Rheumatic Fever went to press, Dr. Raymond Gautier, who had collected and prepared the contributions for publication, died suddenly in Geneva on 19th April, 1957. The further task of preparing an English edition, which he had hoped to do, was by invitation undertaken by us. We have taken the liberty of rearranging some parts of the text and of including a fuller version of Dr. Maxwell Finland's contribution on the *Problems posed by Chemotherapy in Relation to Rheumatic Fever.* We should like to express our indebtedness to Miss W. Gallagher, librarian to St. Mary's Hospital Medical School, for help with the translations and to Miss K. Goff for secretarial assistance.

R. CRUICKSHANK
A. A. GLYNN

CONTENTS

INTRODUCTION

by
DAVID D. RUTSTEIN

International medical meetings, through the opportunities they give for a free exchange of ideas, are most important for the development of mutual understanding. The discussion of medical problems reveals the futility of national and racial differences when confronted with the universality of scientific principles and with the menace of disease.

In this respect the large congresses now so frequent have done useful work. The Conference in which we are now taking part is however a different kind of gathering. In the tradition of the International Children's Centre the meeting is of limited size, gathering together contributors from countries to present and exchange their ideas and experience before an international audience no less qualified who can at the end of the communications freely take part in the discussion.

The Conference is devoted to the *Epidemiology and Prevention of Rheumatic Fever*, and deliberately excludes everything connected with diagnosis and treatment. The programme which has resulted from the collaboration of an eminent physician, Professor Robert Debré, and a liberal layman, M. Pierre Lepaulle, must form a foundation for the research which the International Children's Centre is undertaking on the subject which interests simultaneously paediatricians, bacteriologists, epidemiologists and public health administrators.

Here I would like to take the opportunity of expressing my deep gratitude to Professor Robert Debré and to the Executive Board of the International Children's Centre who took the initiative in organising this Conference and who have invited me to preside. I must also thank the administration of the International Children's Centre for the effective help they have given us, and

Dr. Nathalie P. Masse who has been in charge of the technical organisation of the meetings.

I hope that the debates will enable us to bring to a focus our knowledge of the epidemiology and prevention of rheumatic fever and to draw practical conclusions, as well as ideas for research which we may each pursue in our own countries.

Part I

THE BIOLOGY OF GROUP A HAEMOLYTIC STREPTOCOCCI

GROUP A STREPTOCOCCI IN ACUTE RHEUMATIC FEVER: BACTERIOLOGICAL AND IMMUNOLOGICAL INVESTIGATIONS

by
Robert Wahl

It has been known for some time that a streptococcal infection of the pharynx precedes attacks of acute rheumatic fever. It was gradually established that the causative agent was a well defined type of streptococcus, called at first *Streptococcus pyogenes*, but now more often described by its serological group, *group A* and by one of its most important attributes, that of being *haemolytic*. This variety causes more than 90% of human streptococcal infections (pharyngitis, scarlatina, erysipelas, septicaemia, meningitis, pleurisy, bronchopneumonia, etc.)

I. Bacteriological Study

1. Principal bacteriological characteristics

We do not propose to go into the morphology, cultural appearances, or nutritional requirements of group A streptococci, nor the appropriate culture media. We would, however, point out that blood agar, which is the usual medium for isolation should never be made with human blood, since such media show atypical haemolysis, but with horse, sheep or rabbit blood, and that the blood of the first two can have a raised antistreptolysin O titre. Blood with a titre lower than 100 A.S.O. units/ml. should be chosen. We would add that in certain cases a selective liquid medium containing known amounts of crystal violet, sodium azide and haemolysed horse serum is useful. Most of the other bacterial types can be eliminated with it, but the same medium does not give satisfactory results if agar is added (Wahl & Meyer 1957). Hackenthal and Bierkowski (1951) claim that by using a special medium they were able to separate certain mixed cultures which appeared pure on ordinary blood agar. Cultures, especially on blood agar, should be incubated simultaneously aerobically and anaerobically.

2. Antigens

A distinction should be made between the constituents of the bacterial bodies and the antigens that diffuse out into the culture media. This is a rather rough classification as all products of bacterial metabolism are originally in the bacteria, but it has a practical interest because biologically and immunologically these two categories of antigen play different roles.

a) Antigens in the bacteria

The immunological role of the superficial antigens is well-known. Deep antigens may also exist but knowledge of them is still slight. The group antigen or C antigen is a polysaccharide. The type antigens are proteins. There are over forty different types in group A. Three type antigens M, T, and R. are known and they are distributed differently within the types. M antigen is the most [illegible]

to different types (and so having each its own M antigen) which have a common T antigen. Strains of the same type, i.e. having the same M antigen, but with a different T antigen are also seen though much more rarely. The R Antigen alone is found in type 28 which has no M antigen; serologically it behaves like an M antigen. Little is known about the non-specific antigens. Pakula described one which is also common to certain staphylococci. The deep antigens are only known in very complicated mixtures, such as bacterial extracts obtained by mechanical or by ultrasonic disintegration. This means that their identification is very doubtful and study of them should start again from the beginning. We would mention the extracts obtained by Heidelberger et al. (1931, 1939) and by Lancefield.

b) Antigens diffused into culture media

Dick's erythrogenic toxin does not interest us here. Streptolysin O is common to groups A, C and G streptococci. Hyaluronidase is an enzyme which depolymerizes hyaluronic acid. It is an adaptive enzyme and the addition of hyaluronic acid to the culture medium

increases its production. It is produced by groups A, C, G, L and sometimes B, and by pneumococci and staphylococci. The hyaluronidases of groups A, C and G are antigenically similar to each other The hyaluronidases of pneumococci, staphylococci and group B streptococci are antigenically different. Recent work has shown that in suitable culture media all the types produce hyaluronidase.

Streptokinase is an activator of plasminogen. Its activity is determined by measuring the amount of plasminogen transformed into plasmin, the plasmin being measured by its action on a clot formed by the action of thrombin on fibrinogen.

Streptodornase is a desoxyribonuclease. Protease (Elliott 1954) is the only streptococcal antigen known in a pure crystallized state. Lipoprotease, which has recently been described, splits the lipoprotein compounds of serum, and produces opalescence of culture media containing serum. It is also supposed to be antigenic. A glucuronidase has also been discovered recently.

c) NON-ANTIGENIC CONSTITUENTS AND PRODUCTS OF THE STREPTOCOCCUS

Two of these are important from our point of view: hyaluronic acid and streptolysin S. Hyaluronic acid forms the capsule of the mucoid strains of groups A and C. It plays a slight part in the pathogenicity of group A streptococci and a more important part in that of group C. Streptolysin S is formed by all the group A streptococci and only by them. It is unstable and irreversibly inactivated at a rather low temperature, an acid pH, by oxidation and by some phospholipids in the serum. It is not antigenic.

3. Practical points in the isolation and identification of the group A streptococcus

a. SPECIMEN TAKING AND INOCULATION

Specimens should be obtained either before antibiotics have been administered or after they have been stopped. They should be taken

never be left dry. For inoculation we use the following method: The swab is submerged completely in a tube of the selective medium mentioned above. This is the first inoculation. A drop of this medium is spread on blood agar with a bent glass rod. Figures 1, 3 and 4 show the various methods of inoculating a plate. If, after incubation the inoculation is successful the 3 zones shown on figure 2 will appear. If it is unsuccessful a fresh inoculation is made from the culture in the selective medium.

b. EXAMINATION OF THE CULTURE ON AGAR
for haemolysis and the morphology of colonies.

Haemolysis type β is generally not complete until about 36 or even 48 hours have elapsed. It is often quicker and more complete in anaerobic culture. Very occasionally the group A streptococcus shows incomplete haemolysis (Brown's α type but without greening) especially if the medium has not been properly prepared. Exceptionally there is no haemolysis (fig. 5).

The colonies should be examined under a strong binocular microscope with a stage which can be moved in all directions, under a strong diffused light with the device that we have already described (Wahl and Manigault 1954) As well as the classical colony types, matt, glossy and mucoid (figs. 6-8), variations of the matt type and semi-matt intermediate types are seen (see fig. 9). The last look like mounted pearls. The matt forms produce M antigen, the glossy forms generally produce none or very little. The semi-matt forms are intermediate between these two. The mucoid forms have a hyaluronic acid capsule and generally contain M antigen. Neither the appearance of the colonies nor of haemolysis are in themselves characteristic, but if both these properties are considered together a colony of group A will seldom be missed and that is what matters.

On the other hand, colonies belonging to another group will sometimes be obtained. Another source of error is the presence of *Haemophilus haemolyticus* which produces on horse blood colonies and a type of haemolysis which are practically indistinguishable from those of the streptococcus. A microscopical preparation must then be made to see the difference. However, *Haemophilus haemolyticus* does not haemolyse sheep blood, so that if this is used there is no possibility of error. Several successive subcultures, always from



Fig 1

Classic inoculum
(after a heavy inoculation starting from an initial droplet)

giving for example

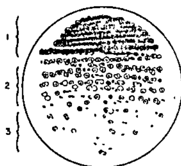


Fig 2

the appearance of growth in 3 diagrammatic zones
(see commentary in text)

Other types of inoculum

employed currently

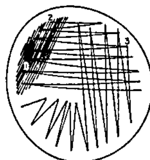


Fig 3

1 = initial heavy inoculum

2 = secondary film of this zone by streaks at 45°.

3 = third starting point of streaks — at first perpendicular to the earlier ones — then dying away on the fourth quarter of the surface

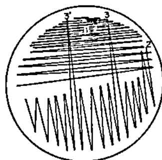


Fig 4

1 = initial heavy inoculum followed by a spread to the middle of the plate, then

2 = second point of departure of perpendicular streaks producing new points at 3 and 3' and final exhaustion



Fig 5
Haemolysis on blood agar
Below, type β (group A strep)
Above, type α without greening
(frequent in other groups, exceptional in group A)



Fig 6 Matt colonies



Fig 7 Glossy colonies



Fig 8 Mucoid colonies



Fig 9 Semi-matt colonies (mounted pearls)

one colony, are necessary before a pure culture for serological identification (group and type) is obtained.

c. Determination of the serological group

In current practice precipitation is done with sera for groups A, C, and G, whose colonies on blood agar look the same. In some cases sera from other groups will have to be used. Lancefield's technique is the most commonly used of the three methods of preparing extracts containing the group antigen. It requires a certain number of technical precautions which we cannot enumerate here. Fuller's method (1938), which is technically a little more difficult has the advantage that it gives fewer cross reactions and can be used with less abundant cultures and on more varied media. Maxted's method (1948) seems to us less sure because it often gives cross reactions. In our view the bacitracin sensitivity test and Hackenthal and Bierkowski's test never take the place of serological group determination. Where the result is doubtful the use of several tests offers an internal control.

d. Determination of the serological type

Type identification is not commonly carried out. It is used only in three kinds of research: Epidemiological investigations, immunological investigations, and the investigations of certain types with special pathogenicity such as type 12 in nephritis. Three methods of type identification are used: agglutination, precipitation, and a method combining the two.

[i] *Agglutination* is produced by both M antigen and T antigen, especially the latter, so that cross agglutination between several types is found. We have seen that M antigen is specific for one type, but T antigen is common to several. Some laboratories use agglutination as a routine diagnostic method by eliminating the group antibodies from the serum. This has the advantage that only agglutinating sera are used and they are much easier to prepare than sera which give both precipitation and agglutination reactions. Exact type identification cannot generally be made this way. Only a series of several types can be indicated amongst which is that of the strain.

[ii] *Precipitation* allows correct identification of the type, but

precipitating sera are difficult to prepare. Strains which have no M antigen cannot be typed although type 28 can be identified by precipitation with its R antigen. Altogether about one third of strains cannot be typed by precipitation.

[iii] *The combined method* seems to be the best. The strain is first classified by agglutination into a group of types which have a common T antigen and then the type is identified by precipitation. This has the advantage of being the least costly and least time-consuming method of identification.

4. Results of investigations on the presence of group A streptococci on the pharynx and nasal fossae of rheumatic fever patients

While sore throat is present it is easy to obtain an almost pure culture of group A streptococci or a considerable number of colonies of this group, but a considerable number of colonies of other bacteria are also present.

During the following days scanty colonies of group A streptococcus are sometimes found amongst a varied flora. They can still be found sometimes after the attack of rheumatism has started. These colonies may be atypical: they may be glossy or only slightly haemolytic. Usually the colonies are typically matt.

In a proportion of cases the streptococcus may disappear rapidly from the pharynx and may no longer be present when the attack of rheumatic fever occurs. There is no doubt that the number of positive findings depends very much on the technique used. With some, the streptococcus is never found after the first phase of sore throat. With the techniques which we have described it can be found in more than 50% of cases of frank rheumatic fever. We do not yet know what significance should be attributed to this finding.

The importance of streptococcal infection of the pharynx before and during the attack has been variously assessed. Some maintain that sore throats that are followed by a rheumatic attack are severer and more prolonged than those that are not
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frequency of rheumatic fever seem to have any connection with the prolonged demonstration of group A streptococci in the throat, whether of the initial type or not.

Here again it is possible that the techniques used in establishing the number of colonies and the persistence of streptococci in the throat were unsatisfactory. A more complete systematic study of the pharyngeal focus of infection would be desirable but is hardly practicable now that penicillin is used systematically in the prevention of rheumatic fever.

II. Immunological Study

The immunological study of streptococcal infections is very difficult because of the multiplicity of streptococcal antigens on the one hand, and, on the other, the absence of sufficiently pure antigenic preparations (with the possible exception of protease). Such preparations are necessary to detect specific antibody reactions by agglutination, precipitation, complement fixation and skin testing. Anti-enzyme antibodies can of course be detected without purified antigens because of the specific action of these enzymes. It should also be remembered that the antigens, non-pathogenic as well as pathogenic, compete in the formation of antibodies. Finally, the presence of most of the antibodies does not indicate the presence of immunity in the sense of resistance to infection, and the amount of antibodies bears no relation to the severity of the infection.

We will consider briefly. antibodies in the serum (circulating antibodies), cutaneous allergic reactions and non-specific serological reactions.

A. Circulating antibodies

In rheumatic fever as in all bacterial infections, the blood contains antibodies against the antigens of the bacterial cells on the one hand, and, on the other, against certain soluble antigens which the bacteria give off into their surroundings. There is no satisfactory technique for the titration of the former. Because of the lack of a pure antigen preparation it is not only impossible to titrate the corresponding antibodies in human serum, but even to distinguish them qualitatively from each other. It is different with the antibodies to the soluble antigens as the corresponding antigens can

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The importance of streptococcal infection of the pharynx before and during the attack has been variously assessed. Some maintain that sore throats that are followed by a rheumatic attack are severer and more prolonged than those that are not. Stetson (1953) does not agree with this. He found, paradoxically, that the proportion of cases of acute rheumatic fever following on sore throats increases as the number of colonies of group A isolated from the throat decreases (the number varying between 1 and 50). Nor did the

frequency of rheumatic fever seem to have any connection with the prolonged demonstration of group A streptococci in the throat, whether of the initial type or not.

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be detected because of their specific action even when they are impure.

ANTIBODIES AGAINST BACTERIAL ANTIGENS

1. Antibodies against superficial antigens

We have already mentioned that the classical reactions, agglutination, precipitation, and complement fixation in the presence of antigen, give unsatisfactory results. Other reactions have been tried but they are still uncertain.

a) ANTI-C ANTIBODIES

According to Rothbard (1945), Watson and others (1946) and Rantz and Randall (1947) precipitation with a fairly pure C antigen is generally negative. Winblad and Edstrom (1948) first studied the agglutination of autoclaved streptococci. Thulin (1948), thinking that the structure of the streptococci might be similar to that of the salmonellae, used the agglutination of streptococci autoclaved at 120° C and attributed it to a thermostable O antigen. Rosendal (1956) supported the view that it is largely due to C antigen and that heating should be at 127° C. to destroy completely the type antigens while still conserving C antigen.

Pakula and Walczak (1955) were unable to demonstrate haemagglutination with C antigen coated on red blood cells. Using Fuller's extract, Kirby (1951) obtained haemagglutination which it was impossible to interpret. Other authors also obtained haemagglutination but it lacked specificity. All the above reactions are positive in some forms of chronic rheumatism. They have been attributed to a non-specific serum protein (Lamond-Havers, 1955) peculiar to chronic rheumatism which is fixed on autoclaved streptococci or red cells sensitized by C antigen. Skillman and others (1954) obtained, with rheumatic serum, haemagglutination of sheep red blood cells sensitized with heat-killed streptococci and agglutination of red cells of rheumatic patients with immunized rabbit serum. Previous treatment with papain increased the intensity of the reaction.

b) ANTI-M ANTIBODIES

Since immunity to streptococcal reinfection seems to be confined to

experimentally. Attempts to precipitate with M antigen give many cross reactions because the present preparations of M antigen are not sufficiently pure (Watson, Rothbard and Swift, 1946; Rantz and Randall, 1947). Thomas (1944) tried without demonstrable results to use precipitation and agglutination to detect anti-M and anti- T antibodies. Nobody seems to have extensively tried inhibition of phagocytosis of living streptococci belonging to the same infective type (Kuttner and Levert, 1944) using human leucocytes. Here the antigen M acts as an antiopsonin.

The bacteriostatic action, which is more marked on strains of the same type as the patient's than on the other types of group A streptococcus (Rothbard, 1945), is difficult to interpret because it is well known that the serum of patients with various acute non-streptococcal infections is also bacteriostatic for group A streptococci (Tillet, 1954). Wannamaker and Denny (1952) consider that the presence of type bacteriostatic antibodies show that there is immunization against this type.

Agglutination of tannin-treated red blood cells sensitized by M antigen described by Denny and others (1954) gives inconsistent results. According to these authors, the reaction could be completed by lysis of the red cells by adding complement, but this reaction was obtained with only one type.

Passive protection of animals with the patient's serum against infection by
siderable pra
test; Watsor
studied the same effect in the monkey. It should be noted that if the serum contains penicillin, protection tests are useless.

c) ANTI-T ANTIBODIES

Thomas 1944 could not demonstrate them by precipitation and agglutination in patients' serum, nor could Lancefield find them.

2. Antibodies against deep antigens

Up till now the only antigens used were not very pure extracts

crushed bacteria, with which precipitation and complement fixation reactions were carried out. These reactions are in no way specific. Such antibodies may play a part in the allergic phenomena of which we will speak later.

ANTIBODIES AGAINST PAKULA'S NON-SPECIFIC ANTIGEN

(an antigen also possessed by staphylococci) contained in Fuller's and Maxted's extracts. They are demonstrated by agglutination of red cells sensitized with these extracts, but the agglutination is not particularly strong in patients infected with streptococci.

3. Study of antibodies by precipitation in agar (Oudin's and Ouchterlony's methods)

The precipitation in agar of each antibody in contact with the corresponding antigen was studied by Halbert, Swick and Sonn (1955) who obtained in rheumatic patients bands of precipitation with all the known streptococcal antigens including erythrogenic toxin. But the same objection applied to this method as to the others because the antigens were not purified. Certain reservations are justified as the reaction was also positive with streptolysin S which is not an antigen.

4. Antibodies against diffusible antigens

a) ERYTHROGENIC ANTITOXIN

This is of no interest in acute rheumatic fever.

b) ANTI-ENZYME ANTIBODIES

Research on anti-enzyme antibodies is much more advanced than on antibacterial antibodies because, as we have said, it is easy to demonstrate the specific action of enzymes even with impure preparations. The existence of antibodies can be demonstrated qualitatively by their inactivating action on these enzymes even when they are impure. On the other hand, titration of these antibodies comes up against considerable difficulties. It should be based on the evaluation of the amount of enzyme inactivated by them, but the methods of measuring these enzymes are very imperfect.

c) AMOUNT OF ANTI-ENZYME ANTIBODIES IN HEALTHY AND INFECTED SUBJECTS

Since the methods of titration of the other anti-enzyme antibodies are so faulty, statistics which give the amount of antistreptolysin O are alone of real value. We will consider them first and we will then compare the theories which are held about the other antibodies in this category.

ANTISTREPTOLYSIN O.

The "normal" values of antistreptolysin O found in subjects who have not had a streptococcal infection for a long time are different in 4 groups (Coburn and Pauli 1932, 1935, Coburn and Young, 1949).

In subjects over 15, in the U.S.A., the normal values are generally below 150 units of antistreptolysin per ml. serum, however, 10% of the "normal" subjects have values of 200 units or over. Bearing in mind our own statistics, we think that values below 150 units per ml. cannot be considered pathological, between 150 or 200 are doubtful; above 200 units per ml. they are probably pathological. According to the Italians and Carraz and Vial (1954), however, the values for normal subjects are as high as 300 units per ml.

Below 6 months they are of the same order as in adults (persistence of maternal antibodies).

In children between 6 months and 3 years the values are very low, quite often non-existent and seldom higher than 50 units per ml. (Rantz and others, 1947)

Between 3 and 15 years the values approach progressively those of the adult.

The differences in the values considered as normal in the various statistics might be explained by differences in the frequency of latent streptococcal infections in the districts in which the authors were working. It is possible, however, that, given larger statistics, these differences would disappear. A further possibility, to which we incline more readily, is that the differences are only apparent and are due to variations in the standard antistreptolysins used.

After group A streptococcal sore throat the antistreptolysin titre starts to rise at the end of the first week. It increases very rapidly and reaches its maximum in 3 to 5 weeks. The average delay in the appearance of the antibody and the curve of the antibody values as

a function of time are the same for all subjets. However, there are very considerable individual variations in the ultimate evolution of the antibody values. Age is one of the most important factors (Solomon 1943). There is a clear difference between the 3-5 year old child and the older subject (Lippard and Johnson, 1935, Rantz and others, 1947). After the age of 3-5 years the values remain constant for several weeks, the speed of their decline is very variable, but it is usually spread over a long period; 6 months to a year. The highest value exceeds 200 units per ml. in 90% of cases. It is often as high as 400 and can even rise to 8,000. However in 10% the antibody values do not rise. Before the age of 3 the average value is not so high. Only in less than 50% of cases does it go above 200 units per ml. In general the maximum value is also lower. However the effect of age is probably only apparent and all the variations, including those which appear to be connected with age, seem to be due to the same causes, which are as follows: a) the degree of previous contact with streptococci: b) the individual capacity for producing antibodies independent of the amount of antigen received: c) the capacity of the infecting strain to produce streptolysin O· and d) the serological type of the infecting strain.

The statistics of rheumatic fever patients gave the opportunity to consider whether they might have a greater capacity than other subjects for manufacturing antibodies. This did not seem to be the case.

OTHER ANTI-ENZYME ANTIBODIES

Some authors have done simultaneous titration of antistreptolysin, antihyaluronidase and antistreptokinase in some subjects. They demonstrated that in general the three antibodies showed a parallel evolution. But in some subjects there are marked differences in the rise of the various antibodies. These differences may be due either to a variation in the ability of the infecting strain to produce the various antigens, or to a selective response by the subject to one or other antigen. The first hypothesis is hardly tenable because the variations in production in vitro of the various antigens are probably only apparent, and if they do exist they probably do not occur in vivo. For instance, it is now known that hyaluronidase is produced in vitro by the strains of all the group A streptococci and not only by types 4 and 12, as was thought before a medium which

was favourable for its production was used. The variations in the production in vitro of streptokinase by various strains observed by Kaplan (1953) are probably due to the same cause. It would therefore seem likely that the differences between the respective values for these various antibodies which have been observed in some subjects are due to individual differences in their capacity for manufacturing one antibody or the other.

There are few reports on antistreptodornase and antiprotease. According to McCarty (1948) antistreptodornase can be demonstrated in only half the subjects. Todd (1947) has studied antiprotease. It is apparently manufactured in very small quantities in man.

INFLUENCE OF ANTIBIOTICS ON THE PRODUCTION OF ANTIBODIES

Administration of penicillin probably decreases considerably the [illegible] diffusible [illegible] verified

B. Cutaneous streptococcal allergy

Cutaneous tests in men and animals have been the subject of numerous older investigations. Lofgren (1951) showed an intradermal reaction in streptococcal erythema nodosum. Swift and Hodge (1936) think that there is a tuberculin type of allergy which produces a reaction to intradermal injection of streptococcal products after a latent period of incubation. These authors maintain that only the whole heat-killed bacterium provokes the allergic reaction. Other authors consider that it can be provoked by various culture filtrates such as those rich in streptokinase-streptodornase, or by fractions of crushed bacteria (perhaps rich in M antigen?) Servi and Pauluzzi (1956) using the intradermal reaction to streptolysin O obtained results which could not be interpreted. In uninfected adults there is often a moderate reaction either to bacteria or to their products (Mackenzie and Hangar, 1927, Howell and Corrigan, 1928). In any case these products are impure and the antigens which [illegible]

whether the intensity of immunity and allergy respectively is a function of the individual reaction of the subjects.

Allergy is not passively transferred by serum (Mackenzie and Hanger, 1930) [illegible] to Chase (1945) [illegible] subject are injec[illegible] [illegible] killed streptococci or streptococcal products are injected intradermally into the same site or elsewhere. This reaction reaches its maximum after a delay of between 3 to 14 days depending on the product injected. The reaction is quicker and shorter in certain subjects who react feebly or when the interval between the two injections is shorter. Recently Lawrence (1955) reproduced the same phenomenon with extracts of leucocytes instead of intact leucocytes and with M antigen instead of bacteria.

REFERENCES

BROWN, J H (1919) The use of blood agar for the study of streptococci Monogr. Rockefeller Inst Med Res No 9
CARRAZ, M and VIAL, J 1954 Determination de taux du l'antihyaluronidase streptococcique et son interet dans le diagnostic de la maladie de Bouillaud. Rev. Lyon Med. 3 673
[illegible] the transfer of cutaneous hypersensitivity to tuberculin.
[illegible] up of streptococcus
[illegible] 33, 651.
[illegible] the response of the

KAPLAN, M H, COONS, A H and DEANE, H. W. (1950) Localisation of antigens in tissue cells J Exp Med *91* 15.

KIRBY, W M M (1951) Hemagglutination reaction in streptococcal infections and acute rheumatic fever Proc Soc Exp Biol *78* 519

KUTTNER, A G. and LEVERT T F. (1944) The occurrence of bacteriostatic properties in the blood of patients after recovery from streptococcal pharyngitis J Clin Invest *23* 151

LAMONT-HAVERS, R W (1955) Nature of serum factors causing agglutination of sensitised sheep cells and group A hemolytic streptococci Proc Soc. Exp Biol *88* 35

LAWRENCE, H S (1952) Cellular transfer in humans of delayed cutaneous reactivity to hemolytic streptococci J Immunol *68* 159

LAWRENCE, H S (1955) Transfer of sensitivity with disrupted leucocytes J Clin Invest *34* 219

LEVINSON, M L. and FRANK, P F (1955) Differentiation of Group A from other beta hemolytic streptococci with bacitracin J Bact *69* 284

LIPPARD, V W and JOHNSON, P (1935) Beta haemolytic streptococcal infection in infancy and childhood Amer J Dis Child *49* 1411

LOFGREN, S (1951) Aetiology and pathogenesis of erythema nodosum and erythema induratum. Nord Med. *46* 1069

MACKENZIE, G M and HANGAR, F M 1927 Allergic reactions to streptococcal antigens J Immunol. *13* 41

MCCARTY, M. (1947) The occurrence during acute infections of a protein not normally present in the blood. J Exp Med *85* 491

MAXTED, W R. (1948) Preparation of streptococcal extracts for Lancefield Grouping. Lancet *2* 255.

MOTE, J R. and JONES, T D (1941) Studies of hemolytic streptococcal antibodies in control groups, rheumatic fever and rheumatoid arthritis J Immunol *41* 35

PAKULA, R and WALCZAK, W (1955) An erythrocyte sensitising factor common to staphylococci and haemolytic streptococci Acta microbiol polon *4* 235

RANTZ [illegible]

TODD, E W (1947) Study of inhibition of streptococcal proteinase by sera of normal and immune animals and of patients infected with group A hemolytic streptococci J. Exper Med 85 591

TITRATION OF STREPTOCOCCAL ANTI-ENZYME ANTIBODIES

by
PIERRE MEYER

These titrations are made by determining by difference the quantity of enzyme inactivated by the corresponding serum antibody. The difficult conditions required are as follows:

(1) **To eliminate all substances capable of interfering with the enzyme-substrate reaction** (certain substances can even induce an auto-catalytic activation). The streptokinase-plasminogen system is particularly sensitive in this respect.

(2) **To establish a relation between the quantity of enzyme present and the quantity of transformed substrate.**

Given that the enzyme-substrate reactions are catalytic in type and do not obey simple quantitative laws, this relation will be empirical. It will hold good, therefore, only under standard operative conditions.

(3) **To adopt a system of reference** in which one of the elements is standardised with a conventional and if possible an international unit. The World Health Organisation should undertake to bring about this standardisation so that the results of different research workers could at last be statistically compared on the epidemiological and prophylactic level which interests us.

TITRATION OF THE ANTI-STREPTOLYSIN O

This is the only one which, at the present time, complies entirely with the requirements that we have enumerated.

(a) **The antigen, Streptolysin O,** belongs specifically to the groups A, C and G. In spite of its great stability, a preliminary choice of the haemolytic dose is necessary at the time of each series of titrations, because of the instability of the other elements of the reaction.

(b) The substrate consists of rabbit red cells. To facilitate reading the haemolysis, we use them at a concentration of 2.25% instead of the generally adopted 5%.

(c) **The standardised unit** - The first Todd unit was a haemolysin unit defined by its haemolytic ability. It has been replaced by an antibody unit given by a hyperimmune horse serum of which 1 ml. contains by definition 20,000 A.S.O. units. Actually each laboratory has only standards adjusted more or less directly to that of Todd. It is not certain that samples of Todd's serum still exist, nor that they have remained stable. It would be useful to compare the different standards used in diverse laboratories in order to fix definitely a single international standard.

TITRATION OF ANTI-STREPTOKINASE

Tillet and Garner (1933), Bertoye and Detolle (1952) and especially Christensen (1940, 1945, 1949) have tried to evolve the best conditions for the reaction by eliminating errors due to interfering substances. These are found in all factors of the reaction:
- an inhibitor of plasmin in streptokinase.
- traces of thrombin in fibrinogen.
- fibrinogen and an inhibitor of plasmin in thrombin and in plasminogen.
- traces of prothrombin in the plasminogen.
- an inhibitor of plasmin in the serum to be examined (removable by inactivation at 56°).
- further, the plasminogen can become inactivated autocatalytically.

How difficult the reaction is to control and how much more so to standardise is evident from the instability of the various com-

ponents and from the fact that no two batches of plasminogen or fibrinogen are identical.

Titration of Anti-Protease

Protease (the only streptococcal antigen obtained in a crystalline state) is produced mostly from strains of Group A.

The method, described by Rotta at the recent congress in Lyons, of titration of specific antibody against protease does not yet appear to be satisfactory.

Titration of Anti-Hyaluronidase

The tests *in vivo* are not quantitative (Maurice 1954) and *in vitro* antibody tests are not standardised (Meyer 1947; Kass and Seastone 1944; Friou 1949; Harris, S. and Harris, T. N. 1949; Harris and Harris 1950; Harris et al. 1949; Schmith and Faber 1950; Carraz and Vial 1954; Faber and Rosendal 1954. The specificity of the reaction depends on the following components:

(a) **The antigen** is specific streptococcal hyaluronidase which differs from testicular and certain clostridial hyaluronidases as well as from hyaluronidase from Groups B, C, G and L streptococci. (Crowley 1944, Leonard *et al.* 1946; Warren *et al.* 1948; Tolksdorf *et al.* 1949; Di Caprio *et al.* 1952 and Faber 1953).

(b) **The substrate** is hyaluronic acid. At the time of preparation and use of batches of different origin, we have been able to confirm the extreme variability of its state of polymerisation. Therefore it is essential to take account, at each test, of the particular behaviour of the preparation used.

(c) **The serum reagent** is usually chosen according to the stock of hyaluronic acid used. In an attempt to standardise it, we have replaced dilutions of horse or rabbit serum, which differ from one batch to another and are spoiled by different interfering substances, by a mixture of albumin and gamma-globulin from known lyophilised stocks.

(d) **The turbidimetric method of dosage** is, in our opinion, preferable to the viscometric or to the Mucin Clot Prevention-test (Friou *et al.* 1947; Harris, T.N. *et al.* 1949; Stoppelman 1950; Werner *et al.* 1951 and Quian *et al.* 1953). We have introduced some modifications to Faber's (1952, 1954) methods.

(e) **Choice of units** – Until now, the results obtained are only comparable if performed by one method from the same laboratory. *In effect, there has been no common measure between the different* procedures, nor even between the results obtained by different authors with the same methods. In addition, there is no definite analogy between the units used in the three methods respectively. However, staking a a basis the numerous relevant works, a very approximate equivalence can be established, recognising that 1 turbidimetric unit equals 0.25–0.50 viscometric units, or 10–80 units Mucin Clot Prevention. If we adopt the turbidimetric method, which seems the best, the technique and the reagents have still to be standardised, before the results may be compared at an epidemiological level.

We come then to the same conclusion for the titration of all the antibodies against streptococcal enzymes: the need for standardisation.

REFERENCES

[illegible]

CHRISTENSEN, L. R. (1945) Streptococcal fibrinolysis, proteolytic reaction due to serum enzyme activated by streptococcal fibrinolysin J Gen Physiol *28* 363

CHRISTENSEN, L. R. (1940) Factors influencing streptococcal fibrinolysin and fibrinolysis J Infect Dis *66* 278

[illegible]

FRIOU, G L. (1949) Hyaluronedase inhibitor in human serum J Infect Dis *84* 240

FRIOU, G. L. and WERNER, H. A (1947 Inhibition of hyaluronidase produced by [illegible]

HARRIS, T N and HARRIS, S. (1949) Streptococcal antihyaluronidase titres in the sera of patients with rheumatic fever. Am. J Med Sci. *217* 174
HARRIS, T N, HARRIS, S and NAGLE, R. L. (1949) Comparison of streptococcal antihyaluronidase with antibodies to other streptococcal antigens in the serum of patients with rheumatic fever and acute streptococcal infection Pediatrics *3* 482.
KASS, E. H and SEASTONE, C V (1944) The role of hyaluronic acid in the virulence of group A hemolytic streptococci J Exp. Med. *79* 319.
LEONARD, S L, PERLMAN, P L and KURZROCK, R. (1946) A turbidimetric method of determining hyaluronidase in semen and tissue extracts Endocrinology *39* 261
MAURICE, P (1954) Le test de dispersion hyaluronidase-hémoglobine dans les états rheumatismaux aigus et chroniques de l'enfance. Acta Pediat. Belg *8* 460
MEYER, K. (1947) Biological significance of hyaluronic acid and hyaluronidase Physiol Rev *27* 335
PIKE, R E (1948) Streptococcal hyaluronic acid and hyaluronidase J. Infect Dis *83* 1
QUINN, R. W, SEASTONE, C. V and WEBER, R. W (1953) Relationship of antigenic characterisation of streptococci and specific antibody response following streptococcal infection J Infect Dis *93* 57
SCHMITH, K and FABER, V (1950) Turbidimetric method for determination of hyaluronidase Scand J Clin Lab Invest. *2* 292.
STOPPELMAN, M R H (1950) Antihyaluronidase content of serum in children suffering from hemolytic streptococcal infection, rheumatic fever and other diseases Acta Pediat *6* 560
TILLET, W. S and GARNER, L (1933) The fibrinolytic activity of hemolytic streptococci J Exp Med. *58* 485
TOLKSDORF, S, MCCREADY, M H, MUCCULLAGH, D R and SCHWENK, E (1949) The turbidimetric assay of hyaluronidase J Lab. Clin Med *34* 75
WARREN, G. H, DURSO, J G and LEVIN, N R. (1948) Modified turbidimetric method for assay of hyaluronidase Endocrinology *34* 48
WERNER, H A, GITSON, D N and JACQUES, R. (1951) Specificity of hyaluronidases formed by several groups of streptococci Proc Soc exp. Biol *76* 585

COMMUNICATIONS

TYPE IDENTIFICATION OF GROUP A STREPTOCOCCI

by

R. E. O. WILLIAMS

Group A streptococci have two type-specific antigens which are called M and T. Both these antigens occur at or near the surface of the coccus, and the M antigen at least can be destroyed by proteolytic digestion without killing the cocci. When cell-wall preparations are made the M antigen can certainly and the T antigen can probably be demonstrated in them. And, when the streptococci are suspended in a specific antiserum either the M or the T antigen can lead to agglutination.

Although it is possible to use either a precipitation or an aggluti-

nation test for recognising both M and T antigen it is usual to use a precipitation test for recognising M and an agglutination test for T. Thanks to the fact that there was a great deal of transatlantic co-operation between Dr. F. Griffith and Dr. R. C. Lancefield in the early days of typing, there is one basic set of strains representing the various types (now some 40 in number), and the strain that has the M antigen known as, say 6, also has its predominant T antigen called 6. And in fact it turns out that the great majority of the streptococci that have the M antigen of one type also have the T antigen with the same number.

The confusing characteristic of the T antigen is that some strains behave as though they had more than one antigen and so are agglutinated by more than one antiserum. From a practical point of view this confusion is greatly mitigated by the fact that, in most cases the patterns are quite stable and are quite reliable for characterizing the strains.

The great advantage of using the T antigen for identifying strains is that it gives a much greater number of positive reactions. Of a total of 2316 strains examined in a 4-year period, only about 1400 (61%) were typable by the precipitation test whereas 2100 (90%) were typable by agglutination.

Now, so far as I know there is no good evidence that rheumatic fever is particularly prone to follow infection by one type any more than by others: there is in fact some, not very good, evidence that it is equally prone to occur after any of a great variety of types.

I say that the evidence is not very good partly because so much of the evidence is based on typing done by the M precipitin test alone, and this test is liable to give 30-50% of untypable strains and in our experience these strains are concentrated on particular agglutination types.

The other fact that makes one wonder whether there may not be some variation between the ability of different strains to produce rheumatic fever is the occurrence of epidemics of rheumatic fever in which 10% or even 15% of the persons with streptococcal infection develop acute rheumatism. It could be that this reflected an effect of the environment rather than of the streptococcus, and it could certainly be that the rheumatogenic characteristic of the streptococcus is not associated with its type. But I feel that we lack

sufficient precise evidence to be certain on this point and I would make a plea for the collection and typing of streptococci, especially from epidemics where the incidence of rheumatic fever is high. And I would add that the streptococci should be characterized by their T antigen as well as by their M antigen: our recent experience with impetigo suggests that the streptococci from this disease have a characteristic T agglutination pattern although they are, for the most part, untypable on the basis of the M precipitation test.

THE CHEMICAL BASIS FOR THE SEROLOGICAL SPECIFICITY OF GROUP A STREPTOCOCCAL CARBOHYDRATE

by

M. McCarty

The group-specific carbohydrate of group A streptococci is composed of the sugars, rhamnose and *N*-acetyl-glucosamine. Studies with Lancefield (1955) have shown that certain variants of group A strains contain a carbohydrate which is serologically different but which is composed of the same two monosaccharides Further study of these two carbohydrates has provided information on the chemical basis for the serological differences and specificity.

Induced enzymes have been obtained from soil bacteria which destroy the serological activity of both carbohydrates. The enzyme which attacks the variant carbohydrate (V enzyme) hydrolyses the antigen to dialyzable products which inhibit the precipitin reaction with rabbit antisera. The inhibitory split products have been identified as rhamnose oligosaccharides, and it is concluded that the specificity of the variant carbohydrate is dependent upon a rhamnose-rhamnose linkage.

The same rhamnose linkage appears to be present in group A carbohydrate, but it is masked so that it does not play an important role in serological activity. The nature of the masking and of the structure responsible for the dominant specificity of the antigen has been determined by studies with the enzyme which acts on the group A carbohydrate (A enzyme). The A enzyme, in the course

of destroying group A reactivity, removes about two-thirds of the total glucosamine of the molecule as free *N*-acetyl-glucosamine. No other end-products appear to be released in significant amounts. The residual carbohydrate remains non-dialyzable, and although it has lost reactivity with group A antisera it now cross-reacts markedly with variant antisera. This cross-reactivity of the treated A carbohydrate can be eliminated by treatment with V enzyme. The findings suggest that the specificity of group A carbohydrate is determined to a large extent by side chains of *N*-acetylglucosamine which also serve to mask underlying rhamnose-rhamnose linkages with V specificity.

It is of interest that the specificity of group A streptococcal carbohydrate depends on a monosaccharide component which is a common constituent of mammalian tissues as well as other bacterial carbohydrates.

REFERENCES

McCarty, M and Lancefield, R. C. (1955) Variation in the group specific carbohydrate of group A streptococci J Exp Med *102*, 11

SOME CLINICAL AND IMMUNOLOGICAL STUDIES ON L FORMS OF GROUP A STREPTOCOCCI

by

W. Hijmans, J. T. Sharp and L. Dienes

Fragility and plasticity have been recognized as properties common to all L forms of bacteria and pleuropneumonia-like organisms since their earliest study. These characteristics have lead most investigators in this field to conclude that this group of microbial agents does not possess a rigid cell wall. Electron micrographs have demonstrated differences in the outer cell membrane of L forms as compared to bacteria, but the chemical nature of this difference has not been defined. In studies on group A streptococci and their L forms which are the subject of this report we have demonstrated that the L form of this species lacks a substance which is a major constituent of the cell wall of the bacterial form

The first table gives the data of one of our experiments. Both the bacteria and their L forms were collected from broth culture and aliquots taken to determine the dry weight, which is shown in the first line of the table. The organisms were extracted with hot acid five times. The extracts were partly deproteinized by alcohol precipitation, concentrated in vacuo, dialyzed against water until chloride free, and their final volume adjusted relative to the original dry weight. These extracts were then examined for the group A polysaccharide by precipitin tests with antisera and for methyl pentose by the Dische and Shettles method. The results are interpreted by us as showing a total absence of the group specific carbohydrate in the L form. In this table the strain of recovered streptococcus is not a direct descendant of the particular L form studied but is a streptococcus recovered from an L form isolated separately from the same bacterial strain.

The second table shows the result of an experiment in which whole cells were examined for rhamnose by paper chromatography. Whereas 1 mg. of bacterial cells gave a strongly positive spot for this sugar, as much as 28.8 mg. of the L form did not contain detectable amounts of rhamnose.

The L forms of three strains of streptococci have been examined for M protein. These strains were selected because they were known to be stable with regard to production of this antigen in the bacterial form. In spite of this selection, only one of the three strains has been found to make the type specific protein in the L form, as judged by the following criteria. Hot acid extracts gave a type specific precipitin reacti [illegible]
parent bacterium, and [illegible]
destroyed by digestion [illegible]
strain has continued to make a detectable amount of M protein after 94 subcultures in the L form. Production of the group specific carbohydrate is a stable property of the bacterial cell. Alteration of this consituent has been reported but total absence has not been observed. For this reason its absence from the L form would appear to be significant. Although no function for this carbohydrate has been established, many polysaccharides contribute, at least in part, to structural rigidity e.g. chitin and celluloses. The group specific carbohydrate has been found to be a major constituent of

the bacterial cell wall. In fact this polysaccharide constitutes from 50-70% of that structure. It, therefore, seems reasonable to propose that the presence of the polysaccharide in the streptococcus might be essential to the rigidity of the bacterium and its absence from the L form might account for the pliability of that form of the organism. It also seems reasonable to propose that such a major alteration in the outer cell membrane might be associated with an alteration in permeability which could account for some of the differences in conditions required for growth.

In contrast to the polysaccharide, production of M protein by the bacterium is a variable property. The finding of this antigen in only 1 out of 3 strains of L form probably only further reflects that variability. It is important to note that the strain which was found to make M protein was also one of those found to lack the carbohydrate thus establishing that the L form did in fact derive from the bacterium.

In summary, two strains of L forms of the group A streptococci have been found to lack the group specific polysaccharide. One of these was found to make M protein. It is suggested that the absence of group specific polysaccharide may be related to the lack of rigidity in the L form.

TABLE 1.

Group specific polysaccharide of group A streptococcal L forms

	Strain AED			*Strain GL 8*	
	Original coccus	L Form	Recovered coccus	Original coccus	L Form
Dry Wt cells extracted in mg	113	270	27	27 2	294
Precipitin with Anti-A sera	POS	NEG	POS	POS.	NEG
Methyl pentose as rhamnose in mg	6.23	0 029	1.32	2.125	0 00
Percent of cells as methyl pentose	5 51	0 011	4 89	7 81	0

TABLE 2.

Paper chromatography on sugar fractions of group A streptococcal L forms

Sample	*Rhamnose*
28 8 mg AED-L 51	Negative
25 0 mg AED-L 102	Negative
30 2 mg Broth media	Negative
1 0 AED streptococcus	Positive

All samples dialyzed, lyophilized, hydrolyzed with 2N HC1, and sugar fraction separated on dowex 50 columns

DISCUSSION

D. D *Rutstein* pointed out that in Rammelkamp's studies on military populations there was no evidence that rheumatic fever occurred more frequently after infection with any particular M type of Group A beta haemolytic streptococcus This contrasts with the previous report from Irvington House where Kuttner found that during epidemics of streptococcal infection of different M types in a population of rheumatic children, there were wide variations in the rate of subsequent recognized clinical attacks of acute rheumatic fever This phenomenon was noted in other rheumatic fever [illegible]
[illegible]
phenomena and not related to specific M types

In contrast to rheumatic fever, the occurrence of acute glomerulo-nephritis following streptococcal infection does seem to be related to particular M types Of these, type 12 is the most common. Other types implicated are type 4, the "Red-Lake strain", and possibly type 25

R, Wahl asked how the group specific carbohydrate was purified?

M McCarty replied that the antigen is prepared from isolated cell walls At present, the cell walls are prepared by disrupting streptococci with glass [illegible]
[illegible]
removal of the enzyme proteins and finally by alcohol and acetone precipitation

R Pakula asked if the soil organisms which hydrolysed the C polysaccharide of streptococci were the same as those which were active against the capsular polysaccharide of pneumococci?

M. McCarty replied that the methods used were much like those used by Dubos in obtaining an organism which hydrolyses the type III pneumococcal polysaccharide. Soil samples were incubated with solutions of carbohydrate, until serological activity disappeared. The organism responsible was isolated by further transfer and plating. Two organisms were isolated: one active against group A carbohydrate and the other against the variant carbohydrate. The enzymes produced are specifically induced by the carbohydrates. The enzymes are obtained in soluble form and concentrated with ammonium sulphate precipitation.

M. Finland wished to know if the L modification was permanent, and whether Dr. Hijmans had isolated L forms from cases of rheumatic fever or rheumatoid arthritis as had been done in the U S A.

E. G. L. Bywaters asked if the L forms which had retained M type specificity could produce type specific antibodies in animals

W. Hijmans replied that nothing was as yet known of any pathological action of L forms or of their ability to induce immunity L forms could revert to the normal bacterial type but lost this property after about ten subcultures Up till now L forms had remained purely subjects of laboratory research.

R. Wahl stressed that in the isolation of streptococci if swabs were not plated out immediately, they must be kept moist The problem of transporting swabs needed further study

R. Cruickshank suggested that a technical improvement in preserving the viability of haemolytic streptococci on nose and throat swabs was the use of serum-coated swabs. These swabs were easily prepared by dipping ordinary cottonwool swabs in undiluted ox serum, drying them in the incubator at 37°C and sterilising at 15 lb pressure

Rubbo and Benjamin in Melbourne had shown that where there was a delay of 24 hours in culturing throat swabs from cases of scarlet fever, the serum-coated swab gave much better results than the ordinary swabs (see Cruickshank, R. Brit med. J (1953) ii 1095). He and his colleagues had found the serum-coated swab very useful in their studies of acute respiratory infections in children.

D. D. Rutstein said that if nose and throat cultures are to be used for the diagnosis of streptococcal infection, a precise definition of a positive culture must be established. As Dr. Wahl had indicated, there must first be a standardization of the technical procedures These include the precision of the swabbing of the nose and throat, the efficient handling of the swab between the taking and the planting of of the culture, the kind of blood used and the other constituents of the culture medium, and the availability of a properly trained and supervised technical staff

A study from Dr. Williams' laboratory (Holmes and Williams, J Hygiene, 1954) showed that "positive cultures" occur in one-fifth of a normal population of children, particularly when they are congregated in schools and nurseries. One might ask—"Do such cultures differ in average number of

colonies from those taken from patients infected with Group A beta-hemolytic streptococcus and is there a critical colony count above which one can be fairly certain of streptococcal infection?" Definite studies on this point are needed before one may recommend the widespread use of methods of culture for beta-hemolytic streptococcus in the prevention of rheumatic fever Such studies will have to be done under controlled conditons on meticulously-followed groups of school children, using exactly the same techniques for well and infected children The results of such studies will do away with the present arbitrary definition of a positive culture which varies from the presence of one colony to a majority of colonies on the plate.

R. Wahl pointed out that counts were not sufficiently precise for an exact estimation of the number of bacteria to be possible. If one tried to define a positive culture, one could consider as such, and as suggesting that the subject was infectious, all cultures giving even one colony of group A

infective for long periods of time.

R. E. O Williams thought that any culture that yielded streptococci in no matter how small numbers, should be regarded as positive. But the significance attached to a positive culture must depend on the reasons for which it was taken If he wished to determine whether a patient under treatment

R Cruickshank agreed with Dr Meyer about the difficulty of comparing results of antibody titres against different components of group A streptococci obtained in different laboratories. He thought it would be difficult to standardise the techniques and suggested that the most *important finding* in using serological methods as indicators of streptococcal infection was a *significant rise in the antibody titre* during convalescence. For example, a 2-tube increase in the anti-streptolysin 0 titre following the acute stage of rheumatic fever would be regarded as evidence of recent streptococcal infection irrespective of the initial titre, which might vary considerably.

P Meyer thought that some doubt remained as to the value of streptococcal antibody determinations In fact there were two distinct fields to consider.

The first was the study of changes in antibody level during an attack. In so far as the antistreptolysin titre was a specific expression of streptococcal infection it was a useful method of following the course of the disease. So would be the titre of other antibodies when their estimation was sufficiently reliable

Secondly there was the epidemiological and statistical study of rheumatic fever with a view to its prevention *There again the antistreptolysin titre* was useful provided everyone took the same standard. A comparison of the different standards used and the adoption of an international one was there-

fore necessary. The use of other anti-enzymes (anti-hyaluronidase, anti-streptokinase, anti-protease) had to be tentative since at present there was no standardisation of substances nor unity of methods in the various laboratories The desirable solution was a summation of several tests so that when everyone spoke the same language epidemiological comparisons might become statistically valuable

R. Debré in closing the discussion alluded to the uncertainty reigning in the minds of clinicians as to what use they could put the information being revealed. The epidemiological problem of rheumatic fever was universal. Its appropriate study necessitated some degree of comparison to ensure that the same streptococci and the same methods of swabbing and of culture were being discussed. The diagnosis and assessment of positive cases had to be uniform. In default of complete standardisation it would be convenient to get agreement on certain conventions. Although the anti-streptolysin determination provided some solid ground this did not hold for other antibodies where again it would be an advantage to have more normal values.

Part II

THE EPIDEMIOLOGY OF INFECTION WITH GROUP A HAEMOLYTIC STREPTOCOCCI

THE EPIDEMIOLOGY OF HAEMOLYTIC STREPTOCOCCAL INFECTIONS

by

PER HEDLUND

Our knowledge of the frequency of beta-haemolytic streptococcal infections has been very considerably extended as a result of investigations made during and following the second world war. The introduction of effective antibiotics and chemotherapeutic agents has significantly helped to throw light on the epidemiology concerned. Important result have been attained by research in many countries, particularly by the systematic investigations carried on in the United States where special attention has been devoted by the Streptococcal Infections Commission of the Armed Forces Epidemiological Board to the channels of propagation. While a great deal of what I have to say constitutes a review of the literature, I shall try to present it on the basis of experience in Sweden.

During an epidemic it is a common observation that a single type or small number of types of group A beta-haemolytic streptococci predominate in the population at a given time. Observations over a long period often show a decline in prevalence of certain types and a rise in others. This was seen in the years 1947 to 1949, when there was a high incidence of scarlet fever and other streptococcal diseases in Stockholm (Hedlund and Lagercrantz 1953).

The material studied consisted of 1,807 cases of scarlet fever In the period April to July 1947 type 6 was predominant with type 5 taking its place in period August to November. Type 6 was also the most common amongst the other streptococcal cases.

In the months of June to August, we see few cases of streptococcal diseases. They appear when the summer vacations are over and the children return to school. The maximum incidence is reached in the winter, usually during February and March.

The survival of beta-haemolytic streptococci in the community seems to depend upon their propagation in man. Lagercrantz found group A beta-haemolytic streptococci in the upper respiratory tract of 10% of healthy blood donors in Sweden examined during the winter season, at a time when there was no epidemic.

The crowding at this boarding school was considerable. In such circumstances the spread of haemolytic streptococci cannot fail to be very general and no person living there could hope to escape coming into contact with the bacteria.

Every person in the school was given penicillin by mouth only, 50,000 units b.d., the same dose for children and adults. The epidemic then ceased and not until three months later did a fresh case of scarlet fever appear. This treatment may perhaps have had the same effect as a school vacation would have had (Watson et al. 1943). These authors found that after a vacation a considerable time was required for streptococcal epidemics to build up again. The Streptococcal Disease Laboratory has found (Wannamaker loc. cit.) that as the length of the carrier state is prolonged, the risk of acquisition among the people around decreases noticeably.

In conjunction with haemolytic streptococcal infections, we speak of bacterial and "toxic" complications. The bacterial complications such as surgical lymphadenitis, otitis, peritonsillitis, [illegible]

tis, myocarditis, nephritis, rheumatic fever and erythema nodosum.

Throughout the course of a scarlet fever epidemic Bengtsson and Birke (1952) investigated eleven hundred cases of tonsillitis and seven hundred and four carriers of haemolytic streptococci. No complications were observed among the carriers, but of the cases with tonsillitis and scarlet fever more than a third developed one or other complication. Only three cases, or two per thousand, developed "bacterial" complications after the use of penicillin therapy compared with 19.2% who developed complications before such treatment was established.

The picture is altogether different with "remote" complications. Despite antibiotic treatment, 4.2% altogether of Bengtsson and Birke's cases were complicated by nephritis, synovitis or rheumatic fever. The frequency of myocarditis was 4.4%. In the "remote" complications age seemed to play an important role, particularly in myocarditis to which adults were 3-4 times more liable than children, and in nephritis.

The most important complications of haemolytic streptococcal infection are rheumatic fever and nephritis. American investigations have shown that about 3% of all persons who have had a haemolytic streptococcal infection will contract rheumatic fever. This figure seems to be remarkably constant but excessive as regards conditions in Sweden. Bengtsson and Birke (loc. cit.) found 1% among 1100 penicillin treated tonsillitis cases. A futher 1% had "synovitis" a disease which is closely related to rheumatic fever. Seegal, Seegal and Jost (1935) have shown that there is little correlation between the occurrence of rheumatic fever and acute nephritis. They compared the figures for admissions with these two diseases at various hospitals in the United States. The incidence of nephritis following scarlet fever varies from year to year. Similarly during the late forties we saw only a few cases in Stockholm but since 1953 there have been many cases of nephritis although streptococcal outbreaks have been minor

A nephritic patient, once he has recovered from his disease shows little tendency to recurrence. He seems to develop an immunity against the nephritogenic agent. There are data indicating that this nephritogenic capacity is linked to some few types of group A streptococci. Type 12 and to a lesser extent type 4 have been shown to be responsible for the majority of cases of acute nephritis in the United States

The good results achieved with penicillin therapy are of major importance in preventing the spread of streptococcal infections. Once penicillin has been used the patients no longer constitute any appreciable danger to their neighbours in hospital. Thus recurrences due to cross infection among patients in hospital have almost entirely disappeared, while secondary cases among the staff are never seen now. On leaving hospital the patient is streptococcal free, and no longer gives rise to secondary or "return" cases outside, as was common before the penicillin era (Ström 1954 see Table 2).

Although the penicillin treated patient is no longer a danger to his environment, the environment may be a danger to him. There are many people with minor streptococcal infections or who are healthy carriers. It is these who are largely responsible for recurrences in patients after their return home.

Control of infection in the environment is therefore a very

TABLE I.

Reduction in "return" cases following penicillin

year	Number of cases	Treatment with Penicillin	Weeks in Hospital	Haem. Strept. on leaving hospital %		Return Cases	
				Throat	Nose	Number	%
1946–47	228	none	6	52	37	10	4 4
1950–51	2148	injection	1	0	0	3	0 13
1950–51	1029	by mouth	1	0	0	2	0 19

important measure, which can now be attained, thanks to penicillin. A case of scarlet fever or sore throat should lead the physician to take such measures. The physician in Sweden is recommended to work along these lines. First he should treat persons with suspected clinical symptoms; in more serious situations he should undertake bacteriological examinations, treat streptococcal carriers and, finally, treat all contacts. In our last big epidemic we obtained good results with this latter method applied to schools and institutions.

Haemolytic streptococcal infections seem to cause type specific immunity. Reinfection with the same type has rarely been reported, and the duration of this type specific immunity in human beings may cover a period of years. The early treatment of streptococcal disease with penicillin lessens this immunity, (Ström loc. cit.) and since the introduction of penicillin we have had an increased number of second attacks or relapses. During the pre-penicillin period these were expressions of cross-infections with different types of haemolytic streptococci rather than of the immunological state. The factors now governing recurrences are the risk of infection from the home environment and also, to some extent, inadequate treatment. If these are dealt with a reduction in the incidence of recurrences should be obtained.

In Stockholm, deferred treatment was adopted, but this involves some risk of allowing rheumatic fever or acute nephritis to develop. To prevent rheumatic fever it is necessary to treat streptococcal infections early and adequately.

REFERENCES

Svenska Lak-Tidn. 43 1055

HEDLUND, P. (1953) Akut vulvo-vaginit vid Streptokockinfektioner. *Nord Med.* 49 566

HEDLUND, P and LAGERCRANTZ, R. (1953) Typing of hemolytic streptococci in scarlet fever and other streptococcal diseases. *Scand. J Clin. Lab Invest.* 5 39

HEDLUND, P and LUNDSTRÖM, R. (1950) Penicillinprofylax under en scarlatinaepidemi. Svenska Lak-Tidn 47 1415

POWERS, G F. and BOISVERT, P L (1944) Age as a factor in streptococcosis *J. Pediat.* 25 481

SEEGAL, D., SEEGAL, E B C and JOST, E. L. (1935) A comparative study of the geographic distribution of rheumatic fever, scarlet fever and acute glomerulonephritis in North America. *Amer J Med Sci* 190 383

STRÖM, J (1954) Penicillin treatment and immunity to Scarlatina *Acta Paediat* 43 267.

COMMUNICATIONS

SOME ASPECTS OF THE EPIDEMIOLOGY OF STREPTOCOCCAL INFECTIONS

by

R. E. O. WILLIAMS

One of the general problems that we shall have to face, more particularly when we come to consider the prevention of rheumatic fever, is the real frequency of streptococcal infections. It is very difficult to get an accurate measure of this in the general population but some figures that we have obtained in a study in a large Children's Home may be of interest.

The Home had between 300 and 500 children, of all ages up to about 15 years, living in separate houses, mostly with 12–15 children in each. We were able to obtain fairly complete records of all the febrile respiratory infections that they suffered, and to examine throat swabs for haemolytic streptococci from practically all the

children who had signs or symptoms suggesting throat infection.

The percentage of all febrile respiratory illness that seemed to be attributable to streptococcal throat infection was approximately 9% among the youngest children, 16% among those aged 3 or 4 years, and 32% among the older children: 25% over all ages. Of all the cases diagnosed as sore throat, about 60% yielded group A streptococci in their throat cultures.

When these figures for streptococcal sore throat are applied to the population at risk we find that the attack rate was just under 1% per month in the youngest group, about 2% per month in the 3-4 year-old children, and about 2.5% per month in the older children.

How do these figures compare with other peoples' experience? Two other reports are worth quoting, although in both cases data for adults as well as children are included. Dingle's studies of families in Cleveland gave rates for streptococcal sore throat of about 1.2% per month, compared with our average rate over all childhood ages of 1.9% per month. Coulter's study of children in 2 towns in New York State again showed a rate of 1% per month for streptococcal sore throat.

We attempted to study the way in which streptococcal infections spread among the children in the "living houses", and in particular the question of the nasal carrier as a source of infection. We may note that, of 94 illnesses for which we thought that we could identify the source, 75% seemed to have been infected from nasal carriers.

The infections tended to occur in small epidemics in the houses. We considered the influence of the primary case in each of these epidemics on the extent of spread. "Precocious spread" was the occurrence of secondary cases within about 5 days of onset of the primary infection, and while the primary case was still away in the hospital; convalescent spread was the occurrence of secondary cases after his return from hospital, in houses which had had no precocious spread.

These results gave a very clear indication of the importance of nasal carriage, and the relative inefficiency of persons infected only in the throat in passing on their infection.

Some streptococcal types were more prevalent than others during one survey. This seemed to be attributable to a large extent to the

fact that the primary cases introducing these types into the cottages were nasal carriers more often than the primaries of other types. Perhaps the "communicability" of a streptococcus, on which Coburn once laid so much stress is really the ability to colonize the

EPIDEMIOLOGY OF STREPTOCOCCAL INFECTIONS IN CZECHOSLOVAKIA

by

K. RASKA

In Czechoslovakia an investigation of the various types of streptococci found in scarlet fever and other streptococcal infections over the last seven years has shown that the prevalence of any streptococcal type changes every three to six months. Of 6158 strains of

Zahradnicky has found streptococcal strains producing an erythrogenic toxin antigenically different from that produced by the standard Dochez N.Y. 5 strain. This could be one reason for the higher incidence of recurrences of scarlet fever in recent years. A second and probably more important reason is the method of treatment introduced in 1949 in all fever hospitals and consisting of penicillin plus a short (6 days) period of hospitalisation. Of 200,000 cases treated in this way we made a special study two years ago of 9121 (Vyborna) and found that scarlet fever had occurred twice in 13.2%, three times in 1.7% and four or more times in 0.4%. The inconvenience of the regime is amply compensated for by the drop in incidence of complications of scarlet fever from 35-65% previously to 4-7% now. The mortality rate fell from 0.3-0.5% to zero. Cases of postscarlatinal nephritis disappeared.

Penicillin is the treatment of choice for scarlet fever and other streptococcal infections as 75% of our strains of streptococci are

sulphonamide resistant. In patients treated by penicillin the incidence of sequelae after streptococcal infections is 6–10 times lower than in those treated with sulphonamides.

As scarlet fever has been studied statistically in Czechoslovakia since 1870 it is possible to follow its epidemiological variations. They may be explained by the profound changes in the way of life of a small country with an increasing density of population and rapidly developing means of communication. This has led over several decades, as in the epidemiology of influenza, to a high degree of herd immunity in the population and thus also to a change in streptococcal infections. A further consequence is that epidemics of scarlet fever in susceptible age groups develop practically at the same time all over the country at intervals of 6–8 years. The epidemic process may be followed more readily in the simplified conditions of rural areas.

R. Cruickshank asked for some information on the erythrogenic toxins with specific antigenicity different from that of the N.Y. 5 strain.

K. Raska replied that the study of different types of erythrogenic toxin had been carried on for four years and would soon end. Numerous cases of scarlet fever had given a skin reaction to standard American toxin during the early days of their illness. These were the sources of group A streptococci used in a study in which different batches of purified toxin were compared in children, both while ill and convalescent, in rabbits and by precipitin tests in agar.

SCARLET FEVER AMONG NURSES OF BLEGDAM HOSPITAL, COPENHAGEN

by

T. Jersild

It has been shown that the treatment of scarlet fever with sulphonamides has no effect on haemolytic streptococci. After eight days of such treatment 73% of cases still grew streptococci whereas only 4% harboured them after six days treatment with penicillin.

Since 1947 all cases of scarlet fever admitted to Blegdam Hospital

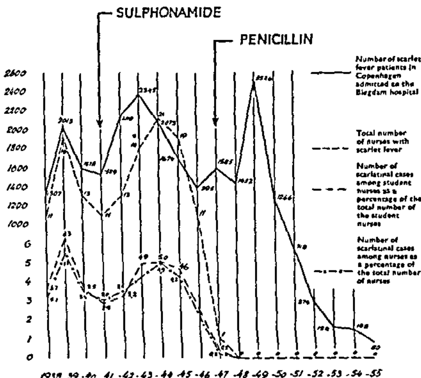


Fig 1 The relation between the number of nurses and the number of admissions, with scarlet fever

have been treated with penicillin As a result one would expect a considerable fall in the number of cases of scarlet fever occurring in the nurses looking after these patients.

Figure 1 gives the annual number of admissions with scarlet fever for the years 1938-1955 as well as the proportion of nurses affected; while Figure 2 gives the number of sick nurse-days in nurses who caught scarlet fever while on duty.

It will be seen that before the employment of penicillin the number of nurses affected depended approximately on the number of admissions with scarlet fever. Thus the years 1938, 1941 and 1946 when the attack rate for nurses was lowest have a correspondingly low admission rate.

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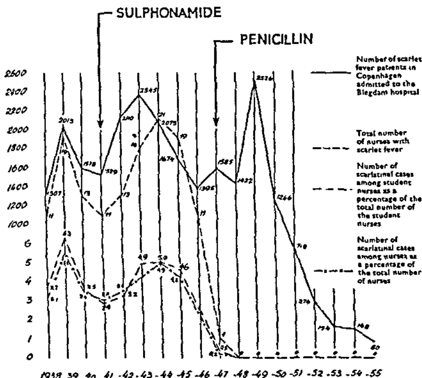


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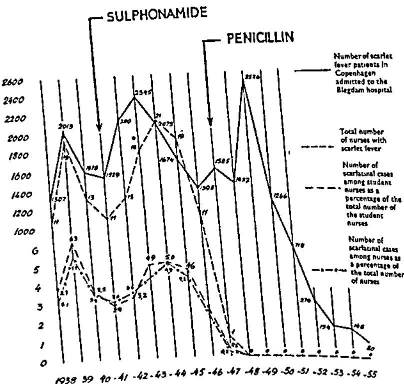


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DISCUSSION

[illegible]

be sensitive to the antibiotic.

P. Hedlund pointed out that this method of treatment could prove ineffective if the streptococcus was associated with a penicillinase producing staphylococcus.

[illegible]

[illegible] signs other than E.C.G. changes and who were probably not all cases of rheumatic fever. The frequency of myocarditis was 2.8% in children and 4.9% in adults. The corresponding figures for acute rheumatic fever were 0.9% and 0.2%.

D. D. Rutstein felt that it was impossible to determine the significance of electrocardiographic changes occurring during the course of scarlet fever when these are unassociated with any other evidence of carditis as defined by the Jones criteria. It may be that patients with such electrocardiographic [illegible] be noted that in the Jones criteria, electrocardiographic change in the form of a prolonged PR interval is included as a minor criterion for diagnosis and not as evidence for carditis which is a major diagnostic criterion.

J. Bogdanowicz reported that in Warsaw the streptococcal type remained practically unchanged throughout the year, and asked if changes had been [illegible]

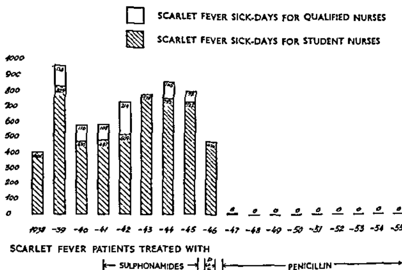


Fig 2. The effect of treatment on time lost by nurses due to scarlet fever.

The figures also show that the number of cases and of days sick among nurses was not reduced through the years 1941 to 1945 although all patients admitted in that period were treated with sulphonamide. In fact scarlet fever reached a peak among nurses in 1944.

On the other hand, beginning with 1947 the year when penicillin was first administered to all patients admitted with scarlet fever, the incidence of scarlet fever among nurses has diminished to such an extent that in that year there was only one case with eight days illness; since 1948 there has been no secondary infection in spite of the fact that the admissions for scarlet fever reached 2,526 in 1949. In 1955 this figure had fallen to 80, most patients being treated at home, a justifiable measure since the rational use of penicillin.

To sum up, the treatment of all cases of scarlet fever with penicillin has considerably reduced the time lost due to scarlet fever among nurses at Blegdam (710 days average/year 1938-45 to 0). This is of particular importance in hospitals with a severe shortage of personnel.

From the epidemiological point of view, wards may be regarded

Part III

THE EPIDEMIOLOGY OF RHEUMATIC FEVER

EVIDENCE FOR THE RELATIONSHIP OF GROUP A STREPTOCOCCAL INFECTIONS TO RHEUMATIC FEVER

by
MACLYN MCCARTY

The concept that streptococcal infections are somehow involved in [illegible]

the advent of bacteriology as a science and consequently before streptococci had been identified as disease producing agents. One of the early clinical observations recorded on this subject appears in the published lectures of Trousseau (1864) which were originally delivered at the Hôtel - Dieu here in Paris almost 100 years ago. He called attention to the fact that articular rheumatism frequently occurs as a sequel to scarlatina. It is clear that he was referring to what we now know as rheumatic fever and not to another illness, such as pyogenic arthritis, since he discusses the *concomitant* occurrence of arthritis, pericarditis and endocarditis. The association in children of St Vitus Dance with this same syndrome is also considered. That Trousseau was not the sole observer who was aware of the apparent relationship between scarlatina and rheumatism is indicated by his frequent references to the comments of Graves on this subject.

Clinicians continued to encounter cases which appeared to confirm these early observations, and the idea was expressed that tonsillitis and septic sore throat, as well as scarlatina, could precede [illegible]

the onset of rheumatic symptoms. Studies of this type were sporadic, however, and wide recognition of the interrelationships was retarded by the low incidence of rheumatic fever in comparison with that of scarlet fever and sore throat. Thus, in large epidemics of scarlet fever, which occurred concomitantly with many other acute diseases, the occurrence of only a relatively small number of cases of rheumatic fever tended to divert attention from any possible etiologic link between them.

In any event, the low incidence of rheumatic fever made it almost impossible to investigate the pathogenesis of the disease by means of systematic epidemiologic studies in the general population. During the major upswing of interest in rheumatic fever which occurred during the third decade of the present century, two new approaches were used in an attempt to obtain more adequately documented epidemiologic information. In the first place, studies were made of closed populations, such as those provided in boarding schools. Secondly, use was made of the fact that in groups of rheumatic children, for example in convalescent homes, the incidence of recurrences of rheumatic fever was extremely high in contrast to the rather low incidence in the general population. It was thus possible to obtain significant data with relatively small groups of patients. The studies made by Glover (1930), Schlesinger (1930), Sheldon (1931), Collis (1931) and Bradley (1932) in England and by Coburn (1931) in the United States are representative of the work carried out during this period. The occurrence of a latent interval between the throat infection and rheumatic fever was confirmed and defined with increased accuracy. It was also demonstrated that the time of peak incidence of rheumatic fever was separated from that of the peak of the tonsillitis epidemic by a period of time which was consistent with the latent interval as observed in individual cases. As the epidemiologic studies were expanded it became apparent that the epidemiology of streptococcal infections followed a pattern almost identical with that of rheumatic fever. For example, the geographic, climatic, seasonal and socioeconomic factors which favoured the occurrence of one disease also appeared to operate in the other. In general, then, the various clinical and epidemiologic studies were in agreement in supporting the view that rheumatic fever is a delayed complication of steptococcal sore throat.

This view was not accepted readily by the medical profession in general, and it is important to examine the reasons for this reluctance. In the first place, rheumatic fever was obviously quite different in nature from known bacterial infections, and there was little precedent for the idea that an acute infection could initiate a continuing process apparently so unrelated to the original disease. Furthermore, the latent interval was distinct enough and sufficiently long to

make some observers doubt that the sore throat participated in the origin of the rheumatic process. This scepticism based on clinical grounds was supported by the confused state of the bacteriology of rheumatic fever and of the classification of streptococci. A number of bacteriologic studies of rheumatic fever had been made, primarily by means of blood culture techniques, and the reported findings proved to be more confusing than helpful since a variety of different bacteria were implicated by different workers as causative agents of the disease. These discrepancies created an atmosphere of doubt concerning all claims for a bacteriological origin of rheumatic fever.

An added difficulty arose from the fact that streptococci, even if one excludes those which are not haemolytic on blood agar, belong to a large and diverse genus of microorganisms. The methods of identification and classification of streptococci available thirty years ago were entirely unsuitable for the type of studies required to provide supporting evidence of the streptococcal origin of rheumatic fever. For this reason, the work of Lancefield (1940-41) on the serological classification of haemolytic streptococci marked an important advance. She showed that streptococci can be divided into a number of distinct groups and that one of these, designated as group A, is primarily responsible for such human illnesses as streptococcal sore throat and scarlet fever. This development greatly improved the potentialities of bacteriologic studies, since it became possible to evaluate more accurately the significance of streptococci found on throat culture.

Despite these improvements in the identification and serologic classification of streptococci, the use of throat cultures proved to be of only limited value in bringing proof to the concept of the streptococcal origin of rheumatic fever. While the study of streptococcal epidemics was made more precise, the results of bacteriologic examination of patients with acute rheumatic fever were equivocal.

[illegible] for this now appears to be referable largely to [illegible] long to [illegible] umber in many cases. Furthermore, patients [illegible] re usually not brought to a clinic where bacteriologic studies can be made

until a week or more after the onset of symptoms. When it is recalled that there was widespread resistance to the view that the streptococcus is the causative agent in scarlet fever, an acute infection which provided generally unequivocal bacteriologic findings, it can be readily understood why bacteriology added little to the acceptance of the views on rheumatic fever. Parenthetically, one might mention the fact that many of those who rejected the concept of the streptococcal nature of scarlet fever recognized the occurrence of a scarlatinal rheumatism, often associated with heart disease, which for some reason they differentiated from rheumatic fever.

While the serologic classification of streptococci failed to lead directly to conclusive bacteriological information in rheumatic fever, this development, together with the new interest in the cellular and extracellular components of group A streptococci, made possible the application of immunological techniques to the problem. The diversity of streptococci, the multiplicity of antigenic components and the lack of suitable differential techniques had vitiated most of the early attempts to obtain immunological information. In the last twenty-five years, however, this approach has been widely and successfully exploited, and the accumulated data provide the most direct and convincing evidence in support of the streptococcal origin of rheumatic fever.

These immunological studies had their origin in the work of Todd (1932) in which he devised a method for measuring antibody directed against the streptococcal hemolysin, streptolysin O. The technique of Todd's test is simple and straightforward, and it has been used successfully throughout the world. As a result, the most extensive serological data available bearing on the relationship of streptococcal infection to rheumatic fever are concerned with the antistreptolysin O determination. In recent years, the findings have been confirmed with other antistreptococcal antibodies, such as antistreptokinase and antihyaluronidase. The nature of these antigen-antibody systems is of considerable importance with [illegible]

[illegible]

largely because of the antigenic heterogeneity and non-specificity of the materials used most of the studies carried out by the classical

techniques of agglutination, precipitation and complement fixation were indeterminate. However, the measurement of antistreptolysin O, antistreptokinase, antihyaluronidase is dependent in each case upon the inhibition of the biological action of an extracellular streptococcal product and specificity is achieved, even with impure antigens, through the use of specific substrates as indicator systems. Thus, lysis of red cells in the case of streptolysin O, lysis of a fibrin clot by plasmin in the case of streptokinase, and hydrolysis of polymerized hyaluronic acid and desoxyribonucleic acid by hyaluronidase and desoxyribonuclease respectively provide the indicator systems whereby the effect of a single antibody is measured even in the presence of a mixture of antigens. The precision of the measurement is subject to the usual limitations of a serum dilution method, but a reasonable degree of accuracy and reproducibility has been achieved when sufficient care is exercised. The determination of antistreptolysin O is the best standardized as well as the most widely employed of these tests, and there is considerable uniformity in the data from various laboratories.

When the antistreptolysin O determination is carried out in groups of patients with proved streptococcal infection, notably streptococcal sore throat and scarlet fever, it is found that 70 to 80 per cent of the patients develop definite increases in titre of the antibody. This figure holds in the case of the vast majority of studies, although there is some indication that infants and very young children respond somewhat less consistently, possibly because of a lack of adequate prior sensitizing experience with the antigen. The increase in titre of antistreptolysin O usually becomes detectable in the second week after the onset of a streptococcal infection and reaches its maximum by the fourth or fifth week. (McCarty 1954)

The pattern of antibody response in rheumatic fever patients (Thomas 1952) has been studied under a variety of conditions, but some of the most useful information for establishing the relationship to streptococcal infection has come from sporadic cases which first come under observation after the onset of symptoms of rheumatic fever. It is under these conditions that rheumatic fever is most frequently seen in clinics serving the general population, and it is of interest that half or less than half of the patients may give an unequivocal history of a recent illness suggestive of streptococcal

infection. In addition, less than half of these patients, when cultured by the usual techniques, appear to harbour significant numbers of group A streptococci in their upper respiratory tract when first seen with rheumatic fever, although this finding may be influenced to some degree by the widespread use of antibacterial drugs. Despite this lack of historical and bacteriologic evidence of a preceding streptococcal infection, patients with early acute rheumatic fever also show a 70–85 per cent incidence of significant elevations in the antistreptolysin O titre. The titre of the serum in rheumatic patients is usually still on the rise during the first week of the disease, an observation which is in accord with the duration of the latent interval (1–3 weeks) and the time required to attain maximal titre in cases of proved streptococcal infection (3–5 weeks). After the maximum level is reached, the titre tends to fall off at much the same rate as it does in the case of patients with uncomplicated streptococcal disease. It is important to note that these findings refer to early rheumatic fever, since if serologic studies are delayed until late or chronic stages of the disease the titre frequently will have returned to normal or near normal levels.

It is apparent that the incidence of antibody response to streptolysin O is as great in sporadic rheumatic fever as it is in proved streptococcal infections In certain studies carried out in large epidemics of streptococcal disease it has been possible to compare directly the response of uncomplicated cases with that of individuals who subsequently develop rheumatic fever. In these investigations there is a suggestion that the incidence of antibody response is actually slightly higher in the rheumatic group. More significantly, however, there is definite evidence from many such studies that the antibody response is quantitatively greater in the rheumatic patient. This does not mean that all patients who develop rheumatic fever have higher titres than all patients with uncomplicated streptococcal disease but rather that the mean maximum titre of the rheumatic group is consistently higher than that of the patients who suffer no delayed complications. The significance of this finding is not clear, although it has been interpreted as indicating hyperreactivity to streptococcal antigens on the part of individuals who are susceptible to rheumatic fever. In any event, it tends to emphasize the importance of immunological data as proof of

the role of streptococci in the etiology of rheumatic fever.

The findings with antistreptolysin O have been duplicated with antistreptokinase and antihyaluronidase. The incidence of significant antibody response is similar to that observed with streptolysin O, and again is at least as high in a group of patients with sporadic rheumatic fever as it is in those with proved streptococcal infection. In addition, the greater mean antibody response on the

veral

extracellular streptococcal antigens, and it is not uncommon to encounter excellent responses to one of the antigens and an absent or equivocal response to the others. As a result of this independence in formation of significant amounts of the several antibodies, it has proved possible to obtain serologic evidence of a preceding streptococcal infection in almost every case of rheumatic fever if more than one antibody is measured. For example, in one study carried out in our laboratory on a group of 23 patients developing rheumatic fever following proved scarlet fever, 83 per cent of the patients showed a response to streptolysin O and 87 per cent to streptokinase, while 96 per cent responded to either one or the other of these antigens (Anderson et al. 1948). The most recent study of this kind was carried out by Stollerman and his colleagues (1956) on a group of sporadic cases of rheumatic fever. It was not possible to determine the *maximum* titre attained in each case, since serum samples were not always available from the earliest stages of the disease. These workers selected 88 patients from whom serum had been obtained within two months of onset of rheumatic symptoms It was shown that 78 per cent of these patients had elevated antistreptolysin O titres while 90 per cent showed a significant response to either streptolysin O or streptococcal hyaluronidase. Antistreptokinase determinations were also carried out, and it was found that 95 per cent of the patients had antibody responses to at least one of the three antigens

It is apparent from these findings that antibody studies have contributed evidence of major importance in establishing the relationship between streptococcal infection and rheumatic fever. Not only is the pattern of antibody response of the rheumatic subject like that of the patient with streptococcal sore throat but

with special effort it appears possible to demonstrate immunological evidence of a preceding streptococcal infection in almost every case of rheumatic fever. Furthermore, there is the striking additional fact that the antibody response is actually quantitatively greater in rheumatic subjects.

The discovery of chemotherapeutic agents effective against haemolytic streptococci made it possible to test their usefulness in the control of rheumatic fever and at the same time to obtain supporting evidence for the relationship of streptococcal infection to rheumatic fever. The first studies on the prevention of rheumatic fever were carried out in populations of rheumatic children. The recurrence rate during the first several years following a proved attack of rheumatic fever is so high that it was feasible to undertake controlled investigations even with relatively small groups of patients. In the earliest work sulphonamides were employed in small daily doses to reduce the risk of acquisition of streptococcal infection, and later when penicillin became available similar experiments were carried out with oral administration of this drug.

The results of many independent evaluations of the prophylactic effect of sulfphonamides and penicillin are in general accord. The recurrences of rheumatic fever in the treated groups were reduced by at least 85 per cent in comparison with control groups. These results are impressive, especially when one considers that there were no good criteria for determining the dosage and regimens to be used in this type of continuous prophylaxis. The system of self-administration of one or more daily oral doses of a drug depends heavily on patient cooperation, and it has become evident that one of the limitations of this method of control of rheumatic recurrences is the uncertainty that adequate amounts of the drug are taken regularly. In recent studies in which patients have been followed by frequent bacteriological and immunological tests, it has been established that when recurrences of rheumatic fever occur under prophylactic treatment evidence of streptococcal infection is obtained with great regularity. Further support for the view that recurrences under prophylaxis are dependent on failure to prevent the acquisition of streptococci comes from the experiments using the long-acting benzathine penicillin by injection at monthly

intervals. By this means, the uncertainties of drug administration are eliminated and an adequate blood level is assured for at least the first three weeks of the month In one of the early studies with the injection of benzathine penicillin, in a group of recently recovered children, there were no recurrences of rheumatic fever in 145 patients over a period of 21 months. These encouraging results have been substantiated in continuing studies. While there is still need for a search for more ideal prophylactic procedures, it can be concluded from the studies so far carried out that if streptococcal infections are prevented there will be no recurrence of rheumatic fever

Evidence of a somewhat different nature has come from investigations of the effect of antibacterial therapy of established streptococcal infections in non-rheumatic populations. In this case, the problem is primarily one of preventing first attacks of rheumatic fever; and consequently much larger groups must be studied to provide conclusive results, since the incidence of rheumatic fever in epidemics of streptococcal disease has generally been found to be 3 per cent or less The outstanding example of this approach is the study of Rammelkamp and his colleagues in a large military establishment These workers encountered epidemics in which streptococcal disease rates were sufficiently high so that thousands of cases were available for analysis. The diagnosis of streptococcal sore throat was confirmed by throat culture, and the follow-up study included clinical observation, serological, and other laboratory tests. Only those cases of rheumatic fever were included which occurred within 35 days of the onset of the sore throat, because the prevalence of streptococci in the population made it likely that cases appearing after this interval could be due to reinfection after discharge from the hospital The results obtained with penicillin treatment are highly significant. Thus, among 996 patients with untreated exudative tonsillitis there were 23 cases of rheumatic fever, while among 978 comparable patients treated adequately with penicillin there was only a single case. This one patient had a history of rheumatic fever in the past, and in addition did not receive treatment until the fifth day after onset of tonsillitis. Comparable results were obtained by the same workers using aureomycin instead of penicillin.

These studies show that it is often possible to prevent rheumatic fever by appropriate antibacterial therapy even after a streptococcal infection has become established. If the organisms are eliminated early in the course of the pharyngeal infection, the chain of events which leads to rheumatic fever is apparently interrupted. It is perhaps significant that the antibiotics which proved effective in these studies also markedly suppress the antibody response to streptococcal antigens. Thus, the protective effect of therapy is accompanied by a decrease in the antigenic stimulus.

In discussing the various kinds of evidence for the relationship of streptococcal infections to rheumatic fever, no mention has so far been made of the experimental production of rheumatic-like lesions in animals. A wide variety of studies have been carried out in different animals using streptococcal vaccines, culture filtrates and live organisms; and the results have in general been evaluated in terms of the histopathology of the lesions produced. Although there have been many claims that these lesions resemble those encountered in human rheumatic fever, there is no unanimity of opinion among pathologists on this point. Murphy (In Thomas 1952) in reviewing the work in this field, concluded that there was no clear evidence that any of the previous workers had produced Aschoff bodies in animals. In his own work with Swift, in which repeated dermal infections with different types of group A streptococci were used in rabbits, Murphy felt that myocardial lesions were produced which closely resemble human Aschoff bodies. Unfortunately, not all pathologists concur in this view, and until better criteria are defined for the relationship of experimental lesions to those of rheumatic fever it does not appear that such animal experiments can be used as proof of the role of the streptococcus in rheumatic fever.

In summary, clinical observations of the relationship between streptococcal disease and rheumatic fever have now been substantiated by several kinds of evidence. Systematic *epidemiological* studies have served to confirm the link between the diseases and to establish that the epidemiology of rheumatic fever is essentially that of streptococcal infections. *Bacteriological* studies have also been helpful, especially by preparing the ground for *serological* investigations. The latter have demonstrated that a specific immune response to streptococcal antigens occurs with great regularity in patients

with rheumatic fever. The *prophylactic* use of antibacterial drugs will prevent recurrences of rheumatic fever in rheumatic subjects, and finally antibiotic *treatment* of streptococcal sore throat can prevent first attacks of the disease. The accumulated evidence clearly implicates infection with group A streptococci as the inciting factor in rheumatic fever.

REFERENCES

ANDERSON, H C, KUNKEL, H G and MCCARTY, M (1948) Quantitative antistreptokinase studies in patients infected with Group A hemolytic streptococci J Clin Invest *27* 425

BRADLEY, W H (1932) Epidemic acute rheumatism in a public school Quart J Med *1* 79

COBURN, A F (1931) The factor of infection in the rheumatic state Williams and Wilkins, Baltimore

COLLIS, W R F (1931) Acute rheumatism and haemolytic streptococci Lancet *1* 1341

GLOVER, J A (1930) Milroy Lectures on the incidence of rheumatic diseases Lancet *1* 499.

HAIG-BROWN, C (1886) Tonsillitis in adolescents London

LANCEFIELD, R C (1940-41) Harvey Lectures, Series 36, 251 (New York)

MCCARTY, M (1954) Streptococcal Infections Columbia University Press, New York

[illegible]

of immune response to group A streptococci to the course of acute chronic and recurrent rheumatic fever Amer J Med *20* 163.

THOMAS, LEWIS, (1952) Rheumatic Fever University of Minnesota Press Minneapolis

TODD, E W (1932) Antigenic streptococcal haemolysin J Exp Med *55* 267

TROUSSEAU, A (1869) Lectures in Clinical Medicine, Vol II The New Sydenham Society, London.

COMMUNICATIONS

TITRATION OF ANTISTREPTOLYSIN O. CRITERIA OF REACTIVITY

by

G. L. DAGUET

Criteria for the diagnostic titre of ASO are not the same for all authors. For example, Todd and Wahl consider 100 U., Green 125 U, Mote and Jones 150 U., Debre, Attal and Drouet and also

Myers 200 U. as normal. The object of this note is to report some simple results of our investigation of over 5,000 titrations carried out in less than a year at the Central Serological Laboratory in the Saint Louis Hospital.

1. Material and Methods

We use the standard streptolysin and antistreptolysin of the Pasteur Institute in Paris following R. Wahl's technique which is derived from that of Todd and Kalbak. The streptolysin, which is reduced by cysteine, is titrated against a half-unit of standard ASO. We noted the amount of streptolysin which produced minimum frank haemolysis. Photometric control showed this degree of haemolysis to be 50%.

Each serum to be examined, diluted 1/50 to 1/3,200 or more, is tested against a minimal haemolytic dose of streptolysin which is estimated each day. After centrifugation the first dilution giving minimum frank haemolysis (50%) is read. As a rule this haemolysis corresponds to a half-unit of ASO per ml. Thus a serum giving 50% haemolysis at 1/400 would have a titre of 200 U. per ml. We cannot stress enough that only fresh sera or those kept in the refrigerator and which are sterile and not haemolysed should be used Altogether the extreme limits of technical variation can be between 1 and 2. We decided to re-assess the criteria of reactivity to allow in part for those variations which may be considered normal. We propose the following criteria:

< 300 U/ml. .. .. no reaction (negative)
> 300 U/ml. < 800 U/ml. . feeble reaction (doubtful)
> 800 U/ml. . ... reaction (positive)

Under the experimental conditions cited above the normal value of 300 U/ml. can in extreme cases go as high as 400 or 600 U/ml. It is important that these apparently wide variations should not completely change the sense of the reaction. It is possible that in an extreme case a normal serum may give a doubtful result.

The level of 800 U/ml. represents for us the frank threshold of positivity and it is only for this figure and upwards that the idea of quantitative measurement can be considered.

2. STATISTICAL AND CLINICAL RESULTS

Of 5,000 sera examined there were:

600 results $\leqslant$ 100 U/ml.	12%
3,000 results 100 to 300 U/ml.	60%
1,050 results $\geqslant$ 800 U/ml.	21%

On the basis of the criteria which we have just formulated, the sera can be classified as follows:

72% no reaction	: normal
7% weak reaction	: doubtful
21% reaction	: positive

Thus the doubtful results, which by definition cannot be taken into account, are reduced to a minimum and are placed between two distinct groups. Thus no serum could pass from positive to negative or vice-versa due to variations in technique alone. These criteria of reactivity were suggested to us by our experimental investigations and by the observations of clinicians who are the best judges of the information provided by titration of ASO.

We have gathered together in table 1 the results of the titration of 210 sera divided into 3 groups: one contains patients with an acute attack of rheumatic fever, the second patients suspected of having rheumatic fever and the third new subjects, mostly adults.

The suggested interpretation of these results is given in table 2. Table 3 gives the values for ASO in the sera of patients suffering from various diseases.

It is not for us to discuss the clinical significance of these results. What is important is to determine whether the values of ASO between 10 and 300 U/ml. really indicate the presence of the antibody. May there not be certain serological factors of unknown origin which inhibit lysis? What significance should be attached to raised values in healthy subjects and to low values in patients at the height of an attack of rheumatic fever?

Close international collaboration between laboratories carrying out these titrations could not but be fruitful. Exchange of standard sera under the auspices of a central laboratory would ensure a standardization of techniques and of their sensitivity and show whether they were reproducible.

TABLE 1.

Results of titration of 3 groups of sera from normals, suspected rheumatic fever and frank rheumatic fever.

Units per ml	Rheumatic fever	Suspected rheumatic fever	Normals	Total	%
$\leqslant 100$	1	15	22	38	18
$> 100 \leqslant 200$	5	12	20	37	18
$> 200 \leqslant 300$	2	5	9	16	
$> 300 \leqslant 600$	4	23	12	39	64
$> 600 < 800$	6	8	2	16	
$\geqslant 800$	52	7	5	64	
Total	70	70	70	210	100

TABLE 2.

Same results as in table 1. Proposed classification.

$\leqslant 300$ U/ml no reaction (negative)
$< 300 > 800$ U/ml : weak reaction (doubtful)
$\geqslant 800$ U/ml · reaction (positive)

Units per ml	Cases				%
	Rheumatic fever	Suspected rheumatic fever	Normals	Total	
$\leqslant 300$	8	32	51	91	43
$> 300 < 800$	10	31	14	55	26
$\leqslant 800$	52	7	5	64	31
Total	70	70	70	210	100

TABLE 3.

ASO titres in various diseases.

Disease	Number of cases	Units ASO ml		
		$\leqslant 300$	$> 300 < 800$	$\geqslant 800$
rheumatism (not rheum fever)	20	18	2	—
nephritis	24	16	6	2
sore throat	11	8	3	
heart disease (adults)	23	18	5	—
scarlet fever	6	4	2	—
chorea	11	3	6	2

R. Wahl mentioned that several authors on the basis of a considerable number of estimations had arrived at more or less the same figure for the upper limit of antistreptolysin in normal subjects. It was around 150 U/ml. Some authors went as high as 250 U/ml. Before admitting that a figure of the order of 800 U/ml was normal further investigation would be necessary. Furthermore it was perhaps unwise to consider as the normal figure the average of titres found in a given statistical collection where the proportion of pathological cases was unknown. Finally, the margin of error indicated was ± 200%; it should be rather of the order of ± 20%.

D. D. Rutstein recalled that a special technique for the titration of ASO had been adopted by 13 laboratories during a concerted Anglo-American study on rheumatism. But as the stock of original serum had been exhausted, different stock sera had had to be used. The titrations carried out at various times produced results which could not be related to a norm. Furthermore, where a series of tests had been done on patients, at different times, the results could not be used for determining whether streptococcal infection had persisted, disappeared or reappeared, during the time the patient had been followed up. The whole question deserved to be re-examined so that a standard technique could be adopted which would permit the establishment of ASO titres which could be reproduced

G. Daguet shared this view because clinicians seemed to attach great value to the results of the titration of ASO and used it in their assessment of the means to be adopted in preventing recurrences. Hence the advantage of standardising the units and the methods of titration so that results from country to country would be comparable. W.H.O. should designate a laboratory which would be entrusted with the preparation of antigens and stock sera with or without lysing antibodies and with the organization of exchanges of information and reagents. Examination of sera gathered in various countries together with epidemiological data would allow the evaluation of the normal threshold of reactivity of ASO.

R. Cruickshank questioned the validity of establishing a connection between the behaviour of ASO and the presence of rheumatism. The fact that the rise of ASO titre was on the average greater in the rheumatic fever patient than in the non-rheumatic indicated a more

pronounced tissue reaction in the rheumatic fever patient but probably did not have any other significance.

D. D. Rutstein reported that studies made at the Rockefeller Institute showed that patients infected with a haemolytic streptococcus of a certain M type had no antibodies against this germ in the early stages of the infection. On the other hand, nearly all the patients suffering from a group A streptococcus infection showed antibodies specific for the type which persisted for a long time. The suggestion might even be made that once these antibodies are formed they never disappear.

STREPTOCOCCAL ANTISTREPTOLYSINS AND ANTIHYALURONIDASES IN RHEUMATIC FEVER

by

J. CHAPTAL, R. JEAN, MME C. CAMPO AND MLLE MARIANI

During the acute stage of rheumatic fever the antistreptolysin titre was over 250 units in 83% of cases and the antihyaluronidase titre was over 8,000 units *in 61%. After a month's treatment with* steroids and antibiotics there was a marked decrease in the ASO titre in 62% of cases; in 25% it was barely changed and in 13% it was raised. The antihyaluronidase titre was lowered in all cases, although in 30% it was still high. After two months' treatment, phenylbutazone having been substituted for the steroids, an ASO titre above 250 units was still found in 25%. *In all but one of the* cases where a third antihyaluronidase estimation was made at this time the titre had continued to go down. We were unable to establish any parallelism between the initial values for these antibodies and the severity of the disease or changes in the biological phenomena (sedimentation rate, fibrinogenaemia, increase in alpha 2 globulin).

The change in the antibody titre under the influence of treatment did not always agree with the clinical evolution of the disease, especially the ASO titre which was sometimes not very high at the start, or was normal during a recurrence after cessation

of treatment, or was still raised at the end of drug treatment although the clinical course may have been favourable.

Under treatment the antihyaluronidase titres followed fairly closely the clinical course, and clinical improvement was accompanied by a fall in these antibodies whatever the original titre. In the acute phase, as in the course during treatment, there is not always parallelism between the ASO and antihyaluronidase titres. The drop during treatment in the antibody titre, especially of antihyaluronidase, seems to be due to the cortisone and not to the penicillin. Finally, very rare but undoubted cases of rheumatic fever are met with in which there is no rise in the streptococcal antibody tire. In conclusion, the lack of a clear parallelism between the various streptococcal antibodies, and the absence of any connection between their titre and the severity of the disease indicated that these antibodies are probably the expression of the causal agent of rheumatic fever but are not the factor responsible for the lesions.

The diagnostic value of titrating streptococcal antibodies is only relative. a definitely raised titre is a point in favour of the diagnosis of rheumatic fever, but a normal titre does not mean that it can be eliminated. The prognostic value of a rise in the initial titre of these antibodies as also of a persistenly raised titre during the course of the disease is absolutely nil. The estimation of several streptococcal antibodies helps to reduce the number of cases of rheumatic fever in which it has been impossible to demonstrate any sign of streptococcal infection. The rare, but undoubted, demonstration of such cases raises the problem of the non-streptococcal origin of some forms of rheumatic fever.

A COMPARATIVE STUDY OF THREE STREPTOCOCCAL ANTIBODIES

by

M. CARRAZ, A. BERTOYE, J VIAL, A L. COURTIEU AND C. GAY

The aim of this work is to determine what advantages derive from the simultaneous estimation of several streptococcal anti-enzymes in the diagnosis of rheumatic fever. The estimation of antistrepto-

lysin O (ASO), antistreptokinase (ASK) and antihyaluronidase (ASH) in the blood has become current practice, but the study of antistreptodornase and antistreptoproteinase is still in the experimental stage.

Various authors have obtained different figures for the first three, there is unanimity on one point only; no one of these antibodies is raised in 100% of cases of developing rheumatic fever. This lack of immunological response usually affects one or more antibodies. By investigating several antibodies together it should therefore be possible to cut down the number of cases which do not give at least one positive result.

We started our investigations in 1954 and since then we have systematically determined the values for ASH of all the sera sent to the Pasteur Institute in Lyons for the titration of ASK (which we have been doing since 1951). In 1,200 combined estimations we found a very definite correlation between the results for both series of titrations.

We used a modified form of Christensen's technique for the estimation of ASK. The results are expressed in multiples of a titre considered as normal (NT). The technique used for titrating ASH is based on Seastone's reaction and is a derivation of the method described by Smith and Faber. The results are expressed in turbidimetric units (TRU).

At the end of 1954 we added the determination of ASO, using the method and reagents of R. Wahl. We discovered that the titration of ASO proved to be a much more sensitive reaction than that of ASK or ASH In fact, it seemed to us to be too sensitive because a considerable number of apparently healthy subjects had a value above the 200 units which constituted the norm

In table I it can be seen that one-fifth of 104 healthy subjects had titres higher than 200 units. This proportion seemed to us to introduce a source of error which was too great and we decided to take into consideration only results of 300 units ASO or above. We give to this titre the same significance as 6 NT for ASK and 20,000 units for ASH.

These form the basis of table II which shows a similar percentage rise in ASK, ASH and ASO in rheumatic fever. It would seem justifiable to conclude that ASK, ASH and ASO behave in an iden-

tical fashion in rheumatic fever. If we call a "positive result" the immunological reactions which reach or pass the figures given above, it is found that only 60% of cases of rheumatic fever give this result. This is obviously due to the standards which we have set. If the sensitivity is only moderate, the specificity is also unsatisfactory, since 10% of patients with various other diseases also showed positive results Any improvement to be obtained from combined titrations should therefore be directed towards sensitivity and specificity.

Table III gives the percentage of positive results in healthy subjects and in patients, based not on the quality of the anti-enzymes but on the number of positive results in each individual If one is satisfied with a positive result for one only of the three antibodies, sensitivity increases but at the expense of specificity. A fifth of the subjects with various other diseases come into this category and 17% of rheumatic fever cases showed no rise in one of the three antibodies. This does not imply that the antibody values in these cases showed no change but that the variations were too small to be considered the result of an attack of rheumatic fever.

If two positive results are deemed necessary, sensitivity is unchanged but specificity is much improved, as the double rise is found in only 4% of subjects with various other diseases and 1% of supposed normals Finally, if all three antibodies are raised the sources of error largely disappear but the sensitivity decreases. All in all, the simultaneous investigation of the three reactions presents the clinician with a blood picture whose interpretation could be of greater help in arriving at a diagnosis than the estimation of one antibody only.

TABLE 1.

ASK ASH and ASO Titres in Normal Subjects.

	Number of normals	ASK NT ASH 10,000 ASO 200	ASK 2 to 6NT ASH· 10,00 to 20,000 ASO 200 to 300	ASK 6 NT ASH· 20,000 ASO 300	ASK>6NT ASH>20,000 ASO>300
ASK	104	75	26	1	2
ASH	104	88	14	2	0
ASL	104	81	16	5	2

TABLE 2.

Frequency of raised ASK ASH & ASO titres in Rheumatic Fever & various diseases.

	Number of cases	ASK raised	ASH raised	ASO raised
rheumatic fever	119	71 (60%)	71 (60%)	71 (60%)
Various diseases	163	16 (10%)	12 (7%)	19 (12%)

TABLE 3.

Simultaneous estimation of 3 antibodies in the same patients

	No antibody raised	1 antibody raised	2 antibodies raised	3 antibodies raised
Normal 104	89%	11%	1%	0
Various diseases 109	78%	22%	4%	0
rheum 119 fever	17%	83%	65%	31%

THE EPIDEMIOLOGY OF RHEUMATIC FEVER IN CHILDREN

by

E. LORENZ

Between 1946 and 1956 259 first attacks and 64 recurrences of rheumatic fever were observed in the Children's Clinic in Graz. There is no doubt that this disease has become much more common in Styria since 1954. The first attack usually occurs between the ages of 7 and 11; up to the age of 14 there is only a slight decrease in its incidence. A study was made of the possible connection between the appearance of rheumatic fever and the presence of streptococci on the mucous membranes. Swabs carefully taken at the start of the first attack were positive in only 35% of cases; 30% of recurrences were positive. The antistreptolysin O titre was consistently raised; usually it was higher than 1:400 and in some cases was as high as 1 6400. It bore no relation to the age of the child

either initially or subsequently. As for the protective action of tonsillectomy, over a period of 8 years a first attack of rheumatic fever occurred in 22 children one to three years after tonsillectomy; of 64 recurrences 16 had had their tonsils removed. These results show that tonsillectomy does not give sufficient protection because it does not prevent either first attacks or recurrences.

THE PROBLEM OF FOCAL INFECTION

by

M. Avcin

The problem of focal infection in children differs from that in the adult. In children it is often connected with infection in the upper air passages It results from and represents a latent, sub-chronic or chronic form of these infections. As children have less specific resistance, the focus can lead to a septic spread with infection or superinfection

Tonsillar foci, especially those on the pharyngeal tonsil, are the most likely cause, but peridontal suppuration or facial sinusitis can also cause trouble.

The examination in Slovenia of 1,275 children aged between 7 and 14 years showed that the tonsils were affected in 35%. The percentage rose to 56 if involvement of the adenoids were included.

There is a striking correlation between the presence of changes in the pharynx and the incidence of rheumatic fever. Of 436 children with rheumatic fever examined at the Children's Clinic in Ljubljana 352 showed focal infection, especially of the tonsils and sinuses, the ratio for these two sites being 10·1.

D. D Rutstein pointed out that it had become increasingly clear over the last 25 years that recurrences of rheumatic fever were caused by an exogenous group A streptococcal infection and not by a strain which had been present for some time in the patient's nasopharynx This theory had received support from studies made in Boston on epidemics of streptococcal infection followed by rheumatic fever, and on the pharyngeal flora of patients between the epidemics. These investigations had lessened interest in the idea

of focal infection as a cause of rheumatic fever. The following question, however, still remains open. Is the persistent rheumatic activity which to is seen in some patients related to continuous focal infection due to haemolytic streptococci? Although the answer is probably in the negative, this question none the less merits further study. It would be necessary to establish whether a streptococcal focal infection was present in a patient with continuing rheumatic activity and whether it was absent where the attacks of rheumatic fever were short.

CHANGES IN THE BONE MARROW IN RHEUMATIC FEVER AND OTHER POSTSTREPTOCCAL CONDITIONS

by

M. Bernheim, Cl. Mouriquand and D. Germain

According to our findings in 130 patients the bone marrow reacts in a constant manner in rheumatic fever in children. Puncture and blood films must be correctly carried out if a valid result is to be obtained. Quantitative changes in particular will show when 1000 nucleated cells are analysed. Whereas normal bone marrow shows only 0.4 to 1% mature plasmocytes, marked elevations of 2.6 to 15% with an average of 5.6% are seen in the acute phase of rheumatic fever. Various elements of the plasma cell series are found: plasmacytes, proplasmocytes, plasmoblasts and tissue plasmocytes. In half the cases there is a definite lymphocytosis, bearing in mind the age of the child.

. The erythroblasts are either normal or lowered (below 10% in a third of cases). Neutrophils are not obviously changed. The eosinophils are often moderately increased. Of these changes, plasmacytosis is therefore the most constant. Its occurrence seems interesting to us for many reasons

Several publications have underlined the connection between plasma cells and immunity, especially the elaboration of globulins and antibodies. In rheumatic fever, therefore, plasmacytosis appears to be the expression of the body's reaction to the streptococcal attack. If a comparison is made with the other biological tests for

rheumatic fever (protein electrophoresis, streptococcal antibody values), it will be found that plasmocytosis is so constant that the [illegible]

[illegible]

streptococcal antibodies. Finally, it mirrors more faithfully the course of the disease, fading rapidly under cortisone treatment and reappearing if there is a recurrence. Thus, plasmacytosis of the marrow, even if it may not be specific for one disease, is the expression of the organism's reaction to attack, in this case by the haemolytic streptococcus. This reaction can be observed directly at its point of origin and not after having been transported elsewhere in the blood.

We found a similar, but less marked, plasmacytosis in 18 out of 32 cases of chorea. This suggests further proof of the rheumatic aetiology of this disease. It is even more marked in scarlet fever where it is accompanied by eosinophilia, but it fades spontaneously in the uncomplicated forms. In our study of 28 cases of acute nephritis of varied aetiology we found plasmacytosis in all, and only in, the children suffering from post-streptococcal glomerulo-nephritis (post-tonsillitis, rheumatic, scarlatinal).

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and the most faithful reflection of, an immunological conflict.

G. *Fanconi* wanted to know: 1) if a similar plasmacytosis was seen in other collagen diseases besides rheumatic fever, and 2) why, since mention was made of changes in the globulins in rheumatic fever, strepto-agglutination was not seen in this disease whereas it was common in the other collagenoses, especially chronic polyarthritis.

D. *Germain* replied that, since their studies were limited to children, they had no experience of marrow changes in chronic polyarthritis. However a recent publication had mentioned more or less marked plasmacytosis in this disease. Where the organism was the site of an immune reaction these changes in the bone marrow were seen, provided that the pathogenic agent was sufficiently aggressive or that the patient reacted with particular

intensity; hence the diagnostic interest of a normal myelogram in a child with suspected rheumatic fever. Abnormal plasmacytosis was also found in a dozen children with primary tuberculosis accompanied by fever and lymph gland reactions. As the causative antigen varied, different humoral reactions could be observed with analogous histological appearances of the bone marrow.

A TEST FOR STREPTOCOCCAL PRECIPITINS

by

PH. LAFONT

The most commonly used serological method for the diagnosis of rheumatic fever is the titration of antistreptolysin. We thought it would be interesting to check the results of this titration by a simple test, since it would appear that even if the results are numerically high, they should not be taken to show the undoubted presence of a persistent streptococcal infection. With this in mind, we turned to the streptococcal precipitin test which is based on the demonstration of antibodies by precipitation on an agar medium after double diffusion (Oakley, 1953; Harris et al., 1955, Halbert et al., 1955). We would like to stress the technique of this test rather than the results as the number of experiments was small.

PREPARATION OF THE ANTIGEN

A group A streptococcus is cultured on the following medium:

Distilled water	1,000 c.c.	Sodium chloride	2.5 g.
Disodium phosphate	8 g.	Magnesium sulphate	0.25 g.
Monopotassium phosphate	0.9 g.	Calcium chloride	0.005 g.
Fibrin peptone	7 g.	Glucose	2 g.
Bacto-casitone Difco	2.5 g.	Phenol red 1%	3 c.c.
Bacto-tryptose Difco	2.5 g.	pH 7.8; sterilisation at 110° for 40 minutes.	

The culture is incubated for 3 days at 37°C., the pH being adjusted each day by adding normal saline. After decanting, ammonium sulphate up to a concentration of 80% is added to the supernatant.

The resulting protein precipitate is taken up in water and dialysed against distilled water for 24 hours. The protein antigen solution should be less than 50 cc. in volume if one litre of culture is used. This complex is preserved by lyophilization.

PERFORMING THE REACTION.

The serum, the 0.3% agar solution to which 0.01% merthiolate has been added, and the antigen complex are placed one on top of the other in a tube 3 mm. in diameter in such a way that the two interfaces are 2 and 3 cm. respectively from the bottom of the tube. The agar (Difco) solution is added with a pipette when it is cooled to about 45°C.

Before adding the antigen the tube is put in the refrigerator so that the layer of agar is set. The tube is sealed and left at room temperature for 3 days. During this time double diffusion takes place in the agar of the constituents of the serum on the one hand and of the antigens on the other. The specific reaction of antigen-antibody precipitation appears then as opalescent zones in the agar. These zones are easily seen if the tube is examined in front of a slit lamp lit by a parallel white light.

RESULTS

1. Sera of patients with acute rheumatic fever

Ten sera obtained during the acute stage of the illness all showed 4 to 7 zones of precipitation and ASO titres varying between 500 and 1,000 units. In three patients with the sequelae of rheumatic fever 2, 2 and 3 zones were observed and the ASO titres were 320, 500 and 960 units.

2. Sera of patients with subacute rheumatic fever

Of 11 cases studied, 10 had ASO titres above 640 units; of these 10, 6 showed 4 or 5 zones of precipitation, 4 showed 2 to 3 zones. In the eleventh case the serum contained only 200 units of ASO but it showed 4 zones of precipitation.

3. Sera of patients with no rheumatic disease or evidence of streptococcal infection

Of 35 sera investigated, none had more than 3 zones of precipita-

tion, but the ASO titre was 320 units in 7 cases, 400 units in 5 cases and 550 units in 2 cases.

4. Sera of patients with albuminuric nephropathy following sore throat

In one case with an ASO titre of 640 units we found 6 zones of precipitation, and 7 zones in another with an ASO titre of 400 units.

These results seem to indicate that the streptococcal precipitin test carried out concurrently with antistreptolysin titration can produce interesting information especially when titration gives numerical results which are difficult to interpret.

REFERENCES

OAKLEY, C L (1953) Antigenic analysis by diffusion J Path Bact *65* 49

HARRIS, T N, HARRIS, S and OGBURN, G A (1955) Gel precipitation of streptococcal culture supernates with sera of patients with rheumatic fever and streptococcal infection Proc Soc Exp Biol (N.Y.) *90* 39.

HALBERT, S P, SWICK, L and SONN, C (1955) The use of precipitin analysis in agar for the study of human streptococcal infections J Exp. Med. *101* 539

DISCUSSION

F. Coste agreed that indirect proof of the connection between the streptococcus and rheumatic fever had been produced However, it would be preferable to have direct proof as already existed for scarlet fever where a pure culture of streptococci had been found in 100% of cases and where it had been possible to reproduce the disease experimentally and where immunity to erythrogenic toxin had been established.

In rheumatic fever, on the other hand, streptococci could be found in only 35% of cases occarding to Lorenz or 50% according to McCarty. Rammelkamp alone had had 100% positive results Was it, perhaps, that streptococcal invasion was less severe in rheumatic fever than in scarlet fever? Or should faulty techniques or the inconsistency and rarity of the streptococcus in the throat be incriminated? Were there findings in human pathology which testified to the particular sensitivity of the rheumatic patient to the streptococcus? Had symptoms of rheumatic fever appeared after the therapeutic use in the United States of vaccines containing haemolytic streptococci?

M. McCarty considered that the disagreement between the figures of positive results could be explained by the fact that Rammelkamp used repeated cultures made in a military environment where streptococcal infection was epidemic. In any case the behaviour of the antibodies had not differed significantly from that of sporadic rheumatism in the civilian population.

There was no proof that the rheumatic patient was particularly susceptible

to streptococcal infection. Skin tests with substances derived from streptococci had not demonstrated clearly any difference in the reacting power of these patients. The fact that rheumatic patients responded to antigen by a production of antibody which was on the average higher than that of the individual with an uncomplicated streptococcal infection was perhaps the [illegible] [illegible] [illegible] non-specific results.

With reference to the lack of correlation between the occurrence of streptococcal infection and rheumatic fever, *M Finland* pointed out that the statistics were based essentially on scarlet fever Only a small proportion of streptococci produced erythrotoxin Once established, immunity to this toxin persisted. Thus, during the spread of streptococcal infections subjects previously exposed to scarlatinal erythrotoxin would have a streptococcal infection but not scarlet fever Consequently the correlation between the total number of scarlet fever and rheumatic fever cases could be only slight, even when the connection between all cases of streptococcal infection and the number of rheumatic fever cases remained constant

With reference to the value of the rise in anti-enzyme titre as a test of clinical streptococcal infection or of rheumatic fever, *A Bertoye* reported that in 90 cases of primary tuberculosis in children a fairly high percentage of raised streptococcal anti-enzyme titres were found, and that these often persisted, as could be seen from the following table

	Anti-enzymes isolated			*Associated anti-enzymes*		
	ASO	*ASH*	*ASK*	*at least 1*	*at least 2*	*at least 3*
number of cases percentage	36 40%	13 14 5%	26 28 5%	46 50%	15 16 5%	6 6 5%

He stressed that the subjects with raised titres showed no sign of streptococcal infection. It would seem as well to bear in mind these findings when interpreting clinically the results of the titration of streptococcal anti-enzymes

Mlle J Labesse thought the following questions should be clarified. Were the reported ASO titres obtained from children hospitalized or in a sanatorium because of their tuberculosis? If this were so, the fact that these places were subject to frequent epidemics of streptococcal infection should be taken into account. Thus at the hospital for children convalescing from rheumatic fever at La Roche Guyon quite a large number of attacks of rheumatic fever had been observed in children hospitalized for primary tuberculosis who had contracted one or more streptococcal infections during their stay *Further, was it certain that a clinical or subclinical haemolytic*

streptococcal infection had been the cause of the raised ASO titres reported? Because a) either it was certain that no haemolytic streptococcal infection could be incriminated, in which case the question of the value of the serological estimation of streptococcal anti-enzymes in subjects with primary tuberculosis would indeed arise: or b) it was not known whether a haemolytic streptococcal infection was current, in which case the rise in the ASO titre of children living in a hospital environment must be attributed, as in normal subjects, until further information were available, to a clinical or inapparent haemolytic streptococcal infection

In some cases of primary tuberculosis *G. Fanconi* had seen manifestations recalling those of rheumatic fever.

R. Debre considered that at the time that tuberculous allergy was established changes were produced which were outside the compass of tuberculosis; such as non-tuberculous bronchitis and rhinitis and various types of infection It was possible that the low ASO titre of the child was raised at this time and this would be a para-allergic manifestation.

[illegible]

lasted were certainly important, but Bywaters had found, at least twice, that a clinical infection by a given type could occur in rheumatic fever convalescents with a rise in the B.S.R. and of the ASO titre even though the bactericidal power of the blood for the specific infection was raised.

M. McCarty thought that Bywaters was reporting for the first time a well-documented case in which re-infection by the same type of streptococcus occurred in a patient in whose blood the presence of antibodies specific [illegible]

that their titre was low and that these antibodies were therefore unable to protect against a massive bacterial infection.

B. Perry asked if it had been shown that rheumatic fever could follow [illegible]

indeed occurred it is probable that streptococci had been present in the throat as well as in the skin or other organs; nothing much could, therefore, be made of these cases in answering the question, owing to the lack of bacteriological and serological proof.

G. Fanconi asked if it was correct to assert that all cases of rheumatic fever were attributable to the streptococcus. He had, in fact, seen cases, sometimes complicated by endocarditis, which had appeared a few weeks after meningococcal meningitis Furthermore typical cases of scarlet fever due to

staphylococci were known It was a question of establishing whether these forms of scarlet fever could produce rheumatic fever

M. McCarty had never seen cases of rheumatic fever after meningococcal meningitis. It was the same problem as that posed by many other illnesses where an attempt had been made to connect them with rheumatism. However, there was no doubt that in the majority of cases the streptococcal infection was the inciting agent. Consequently when other infections seemed to be playing this role it was important to establish if a streptococcal infection had not also been present concurrently The publications which described cases of rheumatic fever following an infection due to a germ other than the streptococcus did not include a bacteriological or serological study which would have excluded the recent presence of the streptococcus As for the cases of scarlet fever which were said to have followed a staphylococcal infection, the few authors who had described them attributed to certain strains of staphylococci the property of elaborating a toxin which induced a rash similar to that produced by the erythrogenic toxin of group A streptococci There was no relationship between staphylococcal infections and rheumatic fever

J Chevallier raised the question whether it was certain that only group A haemolytic streptococci could be responsible for rheumatic fever. He had seen a typical attack with cardiac involvement occurring 15 days after a throat infection which seemed to be due to group C haemolytic streptococci The antistreptolysin titre was raised and a swab of the throat gave a haemolytic streptococcus which grew abundantly in pure culture This proved to be a group C streptococcus and this was confirmed in London. Could we admit that this streptococcus was responsible or should we believe that we had missed a preceding or concomitant infection by a group A streptococcus?

M. McCarty knew of no case of rheumatic fever which might be considered as consequent on infection with group C streptococci. It was, however, clear that pharyngeal infections could occur in which group A could be associated with group C or with other groups As for the specificity of ASO, although the existence of similar haemolysins in other organisms suggested that a rise in antibodies non-specific for group A streptococcal infection might be encountered, there was no evidence that this was a significant practical problem. For example, the pneumococcus was an organism which had its own haemolysin but pneumococcal pneumonia did not cause a rise in ASO titre

In following rheumatic fever patients for a long period of time, McCarty had not encountered any rise of ASO titre after a variety of non-streptococcal illnesses Further support for the specificity of the test was provided by the fact that the formation of ASO kept pace with that of antistreptokinase and antihyaluronidase. Now, there was no question of the non-specificity of these two anti-enzymes In the case of hyaluronidase there was group specificity since group A hyaluronidase differed serologically from that of groups C and G.

E. G. L. Bywaters raised the question of polycyclic rheumatic fever and stressed the difficulty of differentiating reinfection from relapse when the ASO titre is unchanged. *McCarty* considered that polycyclic rheumatic fever represented a variant of chronic rheumatic activity in which exacerbations of disease activity occurred at intervals which could be as long as one [illegible]

[illegible] was to be distinguished clearly from true recurrences.

[illegible] cus. However, the nature of the mechanisms involved in the production of rheumatic fever by streptococcal infection still eluded us, and it was one of the most attractive problems for research. Its solution would help in the better understanding of rheumatism and of its prophylaxis.

FACTORS OTHER THAN STREPTOCOCCAL INFECTION IN THE AETIOLOGY OF RHEUMATIC FEVER

by

E. G. L. Bywaters

As previous speakers have indicated, the most important known factor in the aetiology of rheumatic fever is infection by the group A beta-haemolytic streptococcus: that this is so is shown in a dramatic and undeniable way by the effects of prophylaxis. However, there must be at least one or possibly more factors equally concerned in the causation, since we all repeatedly suffer such infections but only very few of us develop rheumatic fever. From such surveys as those of Rantz, Maroney and di Caprio (1951) it appears that every 100 children develop on the average 50 infections per year with group A streptococcus, or perhaps 25 per year on Dr. Williams' figures. Rheumatic fever affects about 0.05% of the school population per year in notified areas of England and thus we should expect rheumatic fever to follow only once in every 500 or 1000 such infections. If we double this figure to account for the 50% of mitral stenotics with no previous history of rheumatic fever, it is still very small. In epidemics this figure is

increased to perhaps 100 of every 1000 i.e. 10% according to the figures given by Paul compared with 50% in susceptible children (i.e. with previous rheumatic fever).

Why is it that children do not all get rheumatic fever following their biennial attack of streptococcal sore throat? This is the basic question never yet adequately explained. What is the other factor concerned? Presumably this is a host-factor or factors. Is it, in the first place, immunological reactivity? This is impossible to exclude but on the basis of what we know about antibody response, there is no evidence that this is different in the individual case of rheumatic fever from the response following an attack of streptococcal infection without rheumatic sequelae; even in the mass it is no greater than in the group with pyogenic complications without rheumatic sequelae.

The rarity of rheumatic fever below the age of five has been thought to be due to the slow development of antistreptococcal antibody in early childhood, as shown by Quinn et al. (1949) using antihyaluronidase titre. Rantz et al. (1951) showed that the antistreptolysin response was low, short or absent in the very young and only became high or sustained by about the age of 5. If rheumatic fever were thus dependent upon an adult type of antibody response, those few children who did develop rheumatic fever at an earlier age should show a high and sustained antistreptolysin O titre, since they would have had previous multiple antigen stimulation. Indeed figures from Coburn and Pauli (1935) support this, since they show rather higher maximum titres among children aet. 0-7 than in those aet. 8-13 (Fig. 1). Our experience at Taplow is the reverse of this (Fig. 2), since rheumatic fever in the 0-5 age group has a lower titre and the titre increases progressively with age, whether the mean titre (Fig. 3) or the frequency of raised titres (Fig. 4) is considered (Isdale and Holborow, 1956). This resembles more the general pattern of response shown to occur by Rantz in normal non-rheumatic children and does not notably support immunological reactivity as a host factor, although it does not exclude it.

The earliest environmental factor to be blamed was, according to Thomas Sydenham in the seventeenth century, exposure to cold and moisture. It is true that attacks of rheumatic fever are more

A.S.O. TITRES IN 271 R.F. PATIENTS
ACCORDING TO AGE.

AET 0-7
27 CASES
MEDIAN 500

AET 8-13
115 CASES
MEDIAN 333

AET 14-21
72 CASES
MEDIAN 333

AET 22-50
57 CASES
MEDIAN 250

100%
50
0
50-83
100-167
200-333
500-833
1000+

(DATA FROM COBURN & PAULI, 1935)

Fig 1

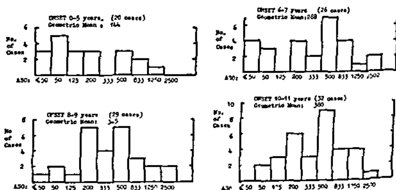


Fig 2 ASO titres in 107 rheumatic fever patients according to age (Data from Isdale and Holborow 1956)

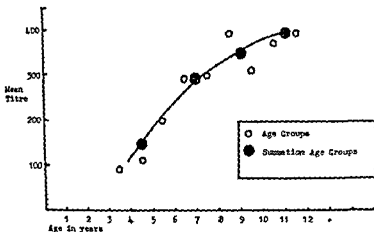


Fig 3 Mean ASO titres in rheumatic fever according to age

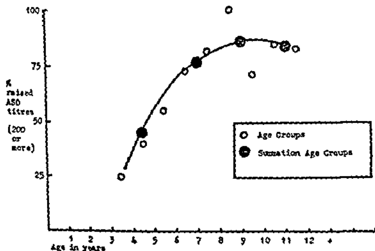


Fig 4 Percentage of raised ASO titres in rheumatic fever according to age

frequent in the colder and moister months of the year, but that is also the period when streptococcal infection is at its maximum and in fact, the rheumatic fever peak usually follows scarlet fever and other indices of streptococcal sore throat infection by a few weeks. [illegible] fever and heart disease mortality [illegible] by Mills of the United States [illegible], [illegible] and *moisture being involved but again these factors probably* [illegible] rate by affecting primarily streptococcal attack rates. What we need to confirm this is comparable surveys of antistreptolysin O titre in various populations, such as we have started to do using cord blood: such surveys would give very useful information on the relative incidence of streptococcal infections. Other studies such as Paul and Dixon's (1937) survey of rheumatic heart disease incidence confirm the effect of cold and moisture. Damp in the sense of geographical relation to waterways within a certain climatic environment does not seem to be so important, despite a widespread popular belief to the contrary.

"Acute rheumatism is essentially a working-class disease: I could count on my fingers the cases I have seen in consultation in 20 years whereas my wards are always full of it" said Robert Hutchison in 1922 Although the complex of poverty with overcrowding, bad housing and malnutrition was more closely associated with rheumatic fever in the past than it is now, at least in Britain and the United States, it is still important both in those countries and elsewhere. The map of England showing deaths from rheumatic heart disease between the ages of 5, 15 and 25 shows a very high mortali[illegible] industrialized areas on Tyneside, South [illegible] 1942). If towns are grouped accord[illegible] same correlation with rheumatic heart disease mortality [illegible] seen (Morris and Titmuss, 1942) and in general, there is a similar difference between social classes whether individual occupations (Emerson, 1928) or grouped occupations (Morris and Titmuss, 1942) are considered.

Many efforts have been made to pinpoint the exact factor in this complex which is responsible. It has long been suspected that overcrowding is one of the most important factors in poverty

from this point of view and studies made in Birmingham by Thompson (1928) and in Bristol by Perry and Roberts (1937) and by Daniel (1942) showed a positive corelation between the density per acre or the number of people per room, and the incidence of rheumatism. Again it may well be argued that overcrowding leads to repeated and more severe streptococcal infections. Thus Holmes and Rubbo (1953) have shown in Melbourne school children that a higher proportion from low rental areas carry

delivered mothers as an index of streptococcal infection in the family unit: there was a significant correlation with social class, and none with the state of parity or whether the children were of school age (unpub. data).

One other study has been made of antistreptolysin titres in families (Hammon et al., 1950). This also showed a higher incidence of increased antistreptolysin titres in low standard families and particularly in those with 3 or more children in the family. The differences between the social classes, however, did not last beyond the age of 9 years.

Malnutrition is also part of the complex of poverty but the evidence for any active role is much less striking than that for overcrowding. Only two claims have been made for specific dietary deficiencies, that of Glazebrook and Thomson (1942) who claimed that Vitamin C supplements abolished rheumatic fever under epidemic conditions and that of Coburn (1945) who claimed that rheumatic fever in school children was greatly decreased by an egg diet. Neither of these claims has been confirmed elsewhere. We may conclude that the effect of poverty is primarily due to overcrowding and the effect of overcrowding is primarily due to an increased streptococcal attack rate.

This leaves only endogenous factors to be considered. There is no evidence yet that those who develop rheumatic fever are endocrinologically or metabolically different from those who do not develop rheumatic fever and it seems likely that their steroid response to infection is the same as that of other children.

Despite this, hereditary disposition has long been recognised as a

possibility. Cheadle in 1889 at Great Ormond Street noted a much greater incidence of rheumatic fever in children with a history of rheumatic fever in their immediate blood relatives. It has, however, been very difficult to separate the effect of the family genes from that of the family environment. May Wilson has claimed from a study of families with rheumatic children that the hereditary factor is an autosomal Mendelian recessive gene which manifests itself in 86% of those hereditarily susceptible i.e. with both parents rheumatic. This has involved, however, considerable manipulation of the figures to allow for the index case and for the varying age of the children. Other studies have shown the same trends but a much smaller proportion of familial rheumatism (Rosenblum and Rosenblum, 1942). More recent studies on the same basis from Yale (Gray et al., 1952) and Mexico City (Salazar-Mallen and Castillo, 1952) have shown results more in line with Wilson's (1940) hypothesis but with a much smaller apparent penetrance, 67% of the susceptible sibs being affected instead of 86% postulated by May Wilson on the basis of her 12 families. Recently May Wilson has re-examined this question by a different approach, using a family study based on selected parents rather than on selected children and has shown that, calculated on a recessive gene basis, the observed number of affected children agrees not unreasonably with the expected number based on parental classification (Wilson and Schweitzer, 1954). Of course a great deal depends upon the criteria on which the diagnosis of rheumatic heart disease is based and it is not clear in May Wilson's studies exactly how much reliance is based solely upon the angle of clearance, a datum which she appears to be alone in using.

Another method of looking at the role of heredity consists of twin studies and in the two reported series by Wilson including Irvine-Jones (1933) and by Kaufman and Scheerer (1938) many more pairs had rheumatic fever in both members of uniovular than of binovular pairs. However, according to May Wilson's hypothesis, at least 86% of the combined uniovular or monozygous twins should show rheumatic fever. In point of fact only 9 pairs out of 31 in the combined series showed this and others, including Perry (1940) have also recorded identical twins with only one member developing rheumatic fever. This is extremely difficult

to explain on a Mendelian recessive theory if a high penetrance is postulated. The apparently increased age-specific attack rates during epidemics of streptococcal infection might lead one to think that there was normally a comparatively low penetrance, capable of being greatly increased in favourable circumstances.

If heredity is concerned and most people would agree that it was, the first place where the infectious organism could meet the inherited tendency is in the upper respiratory tract At Taplow we have shown that if animal or vegetable polysaccharide not normally antigenic is injected into rabbits on the surface of streptococci, antibodies develop to this substance even though the animal's own body contains a similar material (Glynn, Holborow and Johnson, 1956). These are not strictly autoantibodies since they are formed to a hidden aspect of the molecule and do not apparently harm the animal. However, in certain pathological conditions unmasking might occur. It occurred to us that the polysaccharide protein complexes which characterise the secretions of the upper respiratory tract might in fact form such an antigen, and that its variation from person to person due to inheritance might possible form the basis for the hereditary element in rheumatic fever. We have therefore started to determine the hereditary make-up of rheumatic fever and other patients in regard to their red cell phenotype and secretor status, using a new method rendered possible by the coated vaccine technique of Glynn, Holborow and Johnson, and already

A, B or H substance and are hereafter termed non-secretor) is 22% plus or minus a fraction of one per cent, a figure which varies little from place to place. In patients with rheumatic fever we found at

It is difficult perhaps to see what this means 28% of rheumatic fever subjects are non-secretors of ABH substance. 72% secrete it: so what? This is rather like a duodenal ulcer in some respects. However, suppose for example that the rheumatic fever factor was linked with the recessive allelomorph gene for secretion. This

is contained in 22% homozygotes in the general population in double measure and in about 55% heterozygotes in single measure. It can be easily calculated that the incidence of homozygous recessives (i.e. non-secretors) in the rheumatic fever population, i.e. in 78% of the total population is 22/78=28%, a figure very close to the one we have actually found in our rheumatic fever population.

We are planning a family study which would give further data on which to base on explanation of this curious difference of the rheumatic fever population from the normal one.

Meanwhile, we can agree that however important these other factors may *ultimately prove, at the moment* from the practical point of view, they are insignificant beside the factor of Group A streptococcal infection.

REFERENCES

CHEADLE, W B (1889) The Various Manifestations of the Rheumatic State London.
[illegible] Present Status Amer
[illegible]
A-substance J [illegible]
GRAY, F G, QUINN, R W. and QUINN, J P (1952) A Long Term Survey of [illegible] Amer J Med [illegible]
[illegible]
HUTCHISON, R (1922) The Value of Pulse Charts in Acute Carditis [illegible]
Lancet 1 1086
IRVINE-JONES, E (1933) Acute Rheumatism as a Familial Disease. Amer. J Dis. [illegible]
[illegible]

MORRIS, J N and TITMUSS, R. M (1942) Epidemiology of Juvenile Rheumatism. Lancet ii 59

15 177
PERRY, C B and ROBERTS, J A F (1937) A Study of the Variability in the Incidence in Rheumatic Heart Disease within the City of Bristol Brit Med J 2 suppl p. 154
QUINN, R W (1949) The Antihyaluronidase Content of Human Blood Serum J Immunol 61 185
RANTZ, L A, MARONEY, M and DI CAPRIO, J M (1951) Antistreptolysin O Response following Haemolytic Streptococcal Infections in early Childhood Intern Med 87 360
ROSENBLUM, A. and ROSENBLUM, R L (1942) A Study of Seventy Rheumatic Families Amer Ht J 23 71.

WILSON, May G and SCHWEITZER, M D (1954) Rheumatic Fever as a Familial Disease Circulation 10 699

COMMUNICATIONS

SOCIAL FACTORS IN THE AETIOLOGY OF RHEUMATIC FEVER

by

B PERRY

Dr. Bywaters has shown the striking association between rheumatic fever and overcrowding and has suggested that this may be due to the fact that the latter facilitates infection with the haemolytic streptococcus But does this explain it all or is there something other than the streptococcus? The age incidence for rheumatic fever is 5-15 years but first attacks are not only rare before the age of 5, but also after the age of 15, while streptococcal infections are not rare after 15; neither does the immunological response to such infections change in adult life. In the Bristol studies it was shown that the incidence of rheumatic fever

is contained in 22% homozygotes in the general population in *double measure and in about 55% heterozygotes in single measure.* It can be easily calculated that the incidence of homozygous recessives (i.e. non-secretors) in the rheumatic fever population, i.e. in 78% of the total population is 22/78=28%, a figure very close to the one we have actually found in our rheumatic fever population.

We are planning a family study which would give further data on which to base on explanation of this curious difference of the rheumatic fever population from the normal one.

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REFERENCES

450
HUTCHISON, R (1922) The Value of Pulse Charts in Acute Carditis in Childhood. Lancet *1* 1086
IRVINE-JONES, E (1933) Acute Rheumatism as a Familial Disease Amer J Dis. Child *45* 1184
KAUFMAN, O and SCHEERER, E. (1938) Über die Erblichkeit des akuten Gelenkrheumatismus Z Menschl Vereb u. Konstit — Lehre 21 687.
MILLS, C A (1939) Medical Climatology, Thomas, Springfield, Ill.

MORRIS, J N and TITMUSS, R. M. (1942) Epidemiology of Juvenile Rheumatism. Lancet ii 59
PAUL, J R. (1943) The Epidemiology of Rheumatic Fever 2nd Ed Metropolitan Life Insurance Co, New York
PAUL, J R. and DIXON, G L (1937) Climate and Rheumatic Heart Disease J. Amer Med Ass *108* 2096
PERRY, C B (1940) Rheumatic Heart Disease in Identical Twins Arch Dis Child *15* 177
PERRY, C B and ROBERTS, J A F (1937) A Study of the Variability in the Incidence in Rheumatic Heart Disease within the City of Bristol Brit Med J 2 suppl p 154
QUINN, R W (1949) The Antihyaluronidase Content of Human Blood Serum J Immunol *61* 185
RANTZ, L A, MARONEY, M and DI CAPRIO, J M (1951) Antistreptolysin O Response following Haemolytic Streptococcal Infections in early Childhood Intern Med *87* 360
ROSENBLUM, A. and ROSENBLUM, R L (1942) A Study of Seventy Rheumatic Families Amer Ht J *23* 71
SALAZAR-MALLEN, M and CASTILLO, F (1952) Estudios sobre la genetica del

WILSON, May G and SCHWEITZER, M D (1954) Rheumatic Fever as a Familial Disease Circulation *10* 699

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by

B PERRY

Dr. Bywaters has shown the striking association between rheumatic fever and overcrowding and has suggested that this may be due to the fact that the latter facilitates infection with the haemolytic streptococcus But does this explain it all or is there something other than the streptococcus? The age incidence for rheumatic fever is 5-15 years but first attacks are not only rare before the age of 5, but also after the age of 15, while streptococcal infections are not rare after 15; neither does the immunological response to such infections change in adult life. In the Bristol studies it was shown that the incidence of rheumatic fever

in some parts of the City was twenty times as high as in other parts yet the incidence of scarlet fever during the same years was almost uniform throughout the City. Further children who have had rheumatic fever do not invariably develop another attack after a streptococcal sore throat. If the original attack was due to genetic factors surely every sore throat should give rise to a fresh attack of rheumatic fever. Whereas if the development of rheumatic fever is due to some deficiency in the child which is correctable this could be understood.

Coburn's work, which seems never to have been confirmed on the prevention of rheumatic relapses by a good diet may be of importance in this connection. The difference between the patient who makes a complete recovery following a pharyngitis due to the haemolytic streptococcus and the patient who develops rheumatic fever is not absolute but relative. The difference is quantitative and *not qualitative. This is shown by the fact that all grades of illness* occur from the mild "myocarditis' only revealed by a prolongation of the P-R interval in the electrocardiogram, to a rapidly fatal classical attack of acute rheumatic fever.

Finally in Bristol since the war overcrowding has been severe owing to the loss of houses by bombing but the incidence of rheumatic fever has fallen steadily.

A. Wallgren asked why rheumatic fever was widespread in the United States where there was a high standard of living whereas it had become less frequent in Germany during the war.

R. Cruickshank wished to know the role of climate in the genesis of rheumatic fever

B. Perry replied that there were no reliable figures on the incidence of rheumatic fever during the war in Germany but it had certainly fallen in England. The effects of climate were difficult to assess. Severe rheumatic heart disease certainly occurred in the Tropics although acute arthritis was said to be rare.

The high incidence of rheumatic fever in young adults in the United States Armed Forces had no parallel in Great Britain. Green had noticed during the war that naval recruits from a "depressed area" (Tyneside) were more liable to develop rheumatic fever following a streptococcal infection than those from other parts of the country.

K. Raska held that the role of social and genetic factors could only be properly understood after a full epidemiological study. Their work in Czechoslovakia had shown the advantages of pursuing these studies in the simpler conditions of a rural environment. Already it was clear that all factors other than streptococcal infection were of secondary importance.

THE DISTRIBUTION OF RHEUMATIC FEVER IN THE BOLOGNA REGION

by

G. SOTGIU

The regions of Bologna and Padua both have the climate of the plain of the Po but differ economically, Bologna having a higher standard of living. We examined 630 workers in the rice fields and 323 peasants and found 138 cases of uncomplicated rheumatic fever, 117 in the rice workers and 21 in the peasants. In addition there were 32 cases of heart disease with a typical history of rheumatic fever or of upper respiratory infection, again predominantly among the rice workers We found rheumatic fever less frequent in salt workers than in those in gas works or tobacco factories and still less among the fishermen of Rimini. An enquiry among

[illegible]

the finding that rheumatic fever is more likely to affect the heart in children and the joints in adults

Study of rheumatic heart disease in pregnant women showed that while pregnancy often had an adverse effect, with care the mortality could be reduced and premature termination could be used less often.

The observations do not agree with the findings of some British and American authors that rheumatic fever is more common in towns and industrial centres. Around Bologna the disease is particularly widespread in rural areas, where there are unfavourable climatic and economic conditions, dampness and malnutrition.

It is common to find people with "rheumatic" heart disease who

have no history of rheumatic fever but frequent sore throats and attacks of tonsillitis. *Although it is usual to include these in the* rheumatic group, this may not be justified. The clinical differences suggest another aetiology.

The value of antibiotics in the prophylaxis of rheumatic fever is confirmed. No resistant haemolytic streptococci were found.

RHEUMATIC FEVER IN DENMARK

by

T. Jersild

Rheumatic fever has been notifiable in Denmark since 1878. The incidence over the whole country fell from 25 per 10,000 population in 1880 to 3 per 10,000 in 1955. The corresponding figures for Copenhagen are 45 and 3 per 10,000. During the war an increase occurred as in other countries (Figure 1).

Statistics of the sort based on notifications by hospitals and general practitioners are clearly not very reliable. Diagnostic criteria vary, and cases of polyarthritis due to other disease may be included. Some cases especially in earlier years were certainly gonococcal, many others were rheumatoid arthritis of acute onset. These latter causes of error are reduced if one only considers patients under 15 years old. These have been recorded separately since 1906. Among them the frequency of rheumatic fever shows a similar drop to that for the whole population, from 10 cases per 10000 in 1906 to 1.8 in 1955 (Figure 2). The rise during the war is especially obvious.

In conclusion rheumatic fever is becoming a rare disease in Denmark for reasons of which we are ignorant, although it may be said that it is not due to the pasteurisation of milk, which dates from 1920 or to the introduction of sulphonamide or penicillin. Since the beginning of the century the frequency of rheumatic fever has fallen steadily while standrds of public hygiene and of living accommodation have risen. Recently the age distribution of rheumatic fever has changed and the incidence of cardiac complications has fallen from 50 to 15%. Whether these facts are causally related is uncertain but for the time being it seems possible.

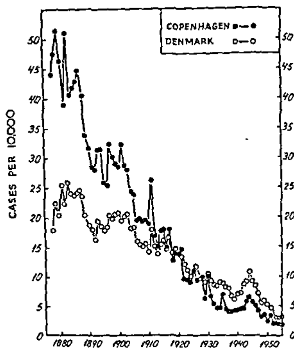


Fig 1. Frequency of rheumatic fever in Denmark and Copenhagen (1878 – 1955)

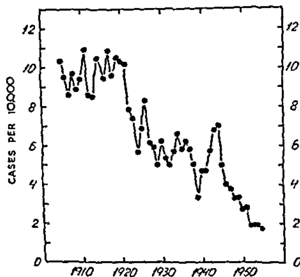


Fig 2 Frequency of rheumatic fever in Denmark (age group 10 – 15 years) (1906 – 1955)

DISCUSSION

J. Wickstrom said that in Finland scarlet fever had been notifiable since 1917, rheumatic fever since 1943. After the first world war the mortality from scarlet fever was very high, today it was almost nil. Since 1950 scarlet fever had been more common than previously whereas rheumatic fever showed a clear tendency to decrease In other words there was no correlation between streptococcal infection and rheumatic fever.

D. D. Rutstein pointed out that in any given epidemic of group A streptococcal infection, one sees all varieties of streptococcal disease, dependent upon such factors as the production of erythrogenic toxin by the infecting strain and the age distribution of the affected population. Thus, there may be in the same household one child with scarlet fever, another with septic sore throat, and an infant with upper respiratory symptoms and otitis media—all apparently caused by the same micro-organism. It is, therefore, important in the study of streptococcal epidemics to recognize all streptococcal infections and not merely those identifiable by the presence of an *erythematous* rash.

Summing up, *Dr. E G. L Bywaters* said· The decreased ASO response in younger age groups with rheumatic fever shown by our results does not *exclude* immunological reactivity as a major factor in aetiology, as I have previously pointed out It does, however, seem to indicate one of two things, either that rheumatic fever is not just a consequence of repeated streptococcal antigen stimulation *or* that if it is a consequence of repeated streptococcal stimulation, the antibodies to its known soluble antigens are probably not concerned. Far too much attention has been paid to these substances and I think that further progress may depend on a study of "cellular antibody".

This discussion has brought out our ignorance of that essential factor which determines whether or not streptococcal infection is going to produce rheumatic fever While present methods of prophylaxis may make this less important than it used to be, there is always a possibility that this situation [illegible] practical application of proph- [illegible] to de- [illegible]

[illegible] Endocrinological studies have [illegible] fully [illegible] creased [illegible] Quite apart from these possible environmental factors, the role of heredity has for long been recognised as an important one it may be that studies on blood group and secretor status, along lines recently developed in relation to duodenal ulcer and which have already shown some difference between rheumatic fever and normal children in our hands, may be important

Part IV

PREVENTION OF RHEUMATIC FEVER

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PROBLEMS POSED BY CHEMOTHERAPY IN RELATION TO RHEUMATIC FEVER

by

MAXWELL FINLAND

The general problem of the use of antibacterial agents in relation to rheumatic fever, particularly as it has been approached and studied in the United States, has involved their use in 5 situations: (1) for the cure of haemolytic streptococcal infections and the possibility thereby of preventing the initiation of attacks of rheumatic fever or their recurrence; (2) for preventing the occurrence of haemolytic streptococcal infections over prolonged periods with a view to preventing recrudescences of acute rheumatic fever in persons already or previously afflicted; (3) in attempts to prevent the development of the streptococcus carrier state or to eliminate the haemolytic streptococcus from carriers, (4) to halt epidemics of haemolytic streptococcal infections in limited population groups, such as military installations, schools, children's homes, and particularly in institutions for the convalescent care of patients who have had rheumatic fever; (5) the prophylactic administration of antibacterial agents in attempts to prevent the occurrence of subacute bacterial endocarditis in patients with valvular heart diseases.

Each of these situations involves the systematic use of antibacterial agents, but the problems posed may vary considerably depending on the particular purpose for which these agents are used. Some of the problems that are involved in all of these situations are, briefly: (1) the choice of the agent which accomplishes the purpose most effectively, (2) the optimum dosage form and regimen for accomplishing this purpose, (3) the acceptability and [illegible]

(b) in their continued use when prolonged administration is undertaken.

The choice of antibacterial agents, whether for the treatment or the prevention of haemolytic streptococcal infections, must be concerned with four major features of the agents:

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The choice of antibacterial agents, whether for the treatment or the prevention of haemolytic streptococcal infections, must be concerned with four major features of the agents·

1. Their effect on the bacteria

This can be measured *in vitro* and is the first and most essential property of the agent selected, for it is generally agreed that both the sulphonamide drugs and the antibiotics, at least in so far as they are used in the treatment of infections, act primarily on the infectious agent. To be sure, the mediation of host factors for the attack on the organisms may be important in the final cure of the infection and in the prevention of recurrences of the original infection or in the prevention of reinfections; and these, in turn, may be related to the activity of the antibacterial agent. With respect to rheumatic fever, this raises the problem of the significance of residual streptococci in the initiation of attacks of rheumatic fever or in causing recrudescences of such attacks.

2. Dosage form and regimen

The form in which the antibacterial agent is given and the dosage regimen employed are important factors that may influence its availability and concentration at the site where the infecting organism is present and multiplying, and hence its effectiveness. The absorption of the agent and its distribution in the body fluids and tissues are therefore important factors Perhaps it is proper also to introduce here the economic factor of the relative cost of the actual application of the different dosage regimens. In this respect it is necessary to consider the total cost, not only of the drug chosen, but of its administration, and not only to the patient but also to the institution or to the public, if they are bearing the costs.

3. Untoward effects

The acceptability of the dosage form and regimen to the patient, and the feasibility of using it in the most effective manner to accomplish the desired purpose are also important. This involves the immediate reactions to the ingestion or injection of the agent as well as the toxic effects that arise from repeated and prolonged administration.

4. Resistance of bacteria to the antimicrobial angets

This may involve 3 factors: (a) The possibility of the development of increasing resistance by the original infecting organism against

the antimicrobial agent in the course of its use in therapy or for prophylaxis; (b) the relative increase in the proportion of resistant strains due to the elimination of sensitive ones; (c) the change in flora, associated with an increase in predominance of more resistant species of pathogenic ones, such as the staphylococcus, or by the overgrowth of organisms such as monilia and coliform bacteria, normally occurring in relatively small numbers as saprophytes, but which may acquire pathogenicity when the common organisms of the normal flora are inhibited.

Data concerning some of these factors are readily available and there is agreement about them. The relative *in vitro* effectiveness of different antibiotic agents against haemolytic streptococci are perhaps the most satisfactory in this regard. Much is also known concerning the absorption and toxicity of the different agents. However, although there are considerable data available on the effectiveness of the different agents and dosage forms, and much of these data have been carefully controlled and documented, there are still considerable differences of opinion as to whether they accomplish the desired goal of eliminating haemolytic streptococci and preventing rheumatic fever and, particularly, whether they prevent the establishment and progression of rheumatic heart disease.

Antibiotic Spectra of the Streptococci

If the major thesis of this seminar is correct, and the main problem in the control of rheumatic fever is the control of streptococcal disease, it may be well to focus on the modern agents available for this purpose. These are primarily the antibiotics, and to a lesser but still important extent, the sulphonamide drugs The rest of this paper will therefore be devoted mainly to the antistreptococcal activity of the antibiotics.

There has been a certain amount of confusion in the recent literature concerning relative activity of the available antibiotics against the streptococcus and also about the changes that may have occurred in the antibiotic susceptibility of streptococci isolated in successive periods,- changes which have been ascribed to the widespread or continuous use of some of the more popular antibiotics. (Adrieu et

al., 1954, Chabbert, 1951, – et al., 1952, Kenney et al., 1953, Kohn et al., 1953, Lund 1952, Lutz & Troussel 1951, Milzer et al., 1948, Rantz & Rantz 1956, Resseler & Bruynoghe 1952, Weil & Stempel 1953, 1955). In some instances some confusion may have been the result of the failure to differentiate the various species and serological groups and types of the streptococci, or, when such differentiation was made, the failure to take these into account, often because of the small numbers of strains involved.

That species differences may be important with respect to antibiotic susceptibility and also with regard to differences in incidence of strains resistant to certain antibiotics was beautifully demonstrated in the case of Proteus, among which strains of the different species show striking differences in susceptibility, particularly to penicillin and the tetracyclines (Potee et al., 1954).

In a previous paper from our laboratory, (Finland et al., 1950) my associates and I presented the results of tests for the *in vitro* susceptibility of different varieties of streptococci to the antibiotics that were available at that time. The strains included had all been isolated and tested in 1949 or earlier and the results were represented graphically in a chart that is reproduced here as Figure 1. In this figure the minimum inhibiting concentrations of the various antibiotics are represented on the horizontal axis (the abscissa) in micrograms per ml. of the test medium, and the cumulative percentage of strains tested with each antibiotic is shown as the vertical axis (ordinate). Each curve in each of the panels represents the results of the tests for sensitivity done with one antibiotic on all of the strains of the variety of the streptococcus indicated. The more uniform the strains are in their sensitivity the more vertical would be the slope of the curve and the smaller would be the upper and lower curved portion which represents essentially the standard deviations. Each panel, therefore, may be termed the antibiotic spectrum of the particular variety of streptococcus represented. The uniformity of the minimum inhibiting concentrations required for different strains of these organisms to any one antibiotic would be reflected in the shape of the individual curve representing that antibiotic. The relative susceptibility of all the strains to the different antibiotics can be clearly seen from the relative position of the different curves, those to the left re-

presenting the most active and those to the right the least active of the antibiotics.

In the lowest panel of this figure one can see clearly the quantitative differences in the action of the various antibiotics on all of the strains of beta haemolytic streptococci (excluding the haemolytic enterococci). This is particularly evident from the clear separation and spread of the curves across the chart. One may also observe the rather uniform sensitivity of the different strains by the steepness of the individual curves. The lower panel of this chart, therefore, shows that the order of effectiveness of these antibiotics against *Streptococcus pyogenes*, as judged from these *in vitro* tests, is as follows: 1. penicillin, 2. bacitracin, 3. Aureomycin (chlortetracycline), 4. Chloromycetin (chloramphenicol), 5. streptomycin, 6. Aerosporin (polymyxin B) and 7. polymyxin (polymyxin D).[1])

The middle panel of Figure 1 depicts the results of the tests for sensitivity of strains of *Streptococcus viridans*, including both alpha haemolytic and nonhaemolytic (gamma) strains. The greater variation in the sensitivity of the different viridans strains is evident from the more gradual slope of the curves for penicillin, Aureomycin and streptomycin. These

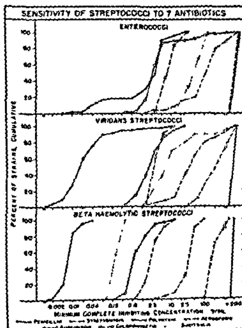


Fig. 1 Reproduced from Finland, Wilcox and Frank (1950). These streptococci were all isolated and tested in 1949 or earlier

[1]) Polymyxin D was being investigated at that time but is no longer available and hence was not used in the subsequent studies to be presented.

curves are based on the results of appreciably larger numbers of strains than were those representing the remaining antibiotics, but the curve for bacitracin also shows a similar difference. In addition to the greater variation among the viridans strains in their sensitivity to the individual antibiotics, there were also quantitative differences in the sensitivity of the majority of strains, particularly to penicillin and bacitracin. The greater susceptibility of the beta haemolytic streptococci to these two antibiotics is evident from the further position to the left of the curves in the lower panel when compared with the corresponding ones in the middle panel. The same is true, but to a less extent, in the case of Aureomycin and Chloromycetin. The order of effectiveness of the different antibiotics against the viridans streptococci, based on these data, is as follows: 1. penicillin, 2. Aureomycin, 3. Chloromycetin, 4. bacitracin, 5. streptomycin, 6. Aerosporin and 7. polymyxin (D). Except for the position of bacitracin, therefore, this order is similar to that noted for beta haemolytic streptococcus.

The results of all the sensitivity tests carried out on strains of enterococci are shown graphically in the upper panel of Figure 1. Of particular interest in this figure is the curve representing the penicillin sensitivity of the strains, which indicates a fairly wide spread. Although on a weight basis penicillin was still the most effective agent *in vitro* against enterococci, there were very few strains that were susceptible to concentrations which inhibited most of the haemolytic or viridans strains of streptococci. Of some interest also was a small percentage of strains that were relatively resistant to Aureomycin, although the great majority of strains were quite similar to the other kinds of streptococci in their sensitivity to this antibiotic. Chloromycetin, on a weight basis, was appreciably less effective than Aureomycin against most strains.

The order of effectiveness of the various antibiotics against the enterococci, as judged from these *in vitro* data, was as follows: 1. penicillin, 2. Aureomycin, 3. Chloromycetin, 4. bacitracin, 5. streptomycin, 6. Aerosporin and 7. polymyxin. This order is the same as that noted for the viridans strains.

We have now reinvestigated the problem with respect to strains of haemolytic streptococci isolated more recently; these were tested with 6 of the same antibiotics (all except polymyxin D) and

with 5 additional ones which have become available and have been accepted for general use since 1949. This was undertaken with the following objectives: 1. to determine the relative susceptibility of more recently isolated strains to currently available and useful antibiotics, 2. to determine whether this susceptibility varies with the different groups or types of haemolytic streptococci and 3. to learn, if possible, whether there has been any change in the susceptibility of the streptococci to any of the antibiotics since the earlier study.

Antibiotic Spectrum of Non-Group D Haemolytic Streptococci

The results of tests done with 11 antibiotics on 394 strains of non-group D haemolytic streptococci isolated between December 1953 and March 1955 are shown in Figure 2. The strains were derived from cultures of throat swabs and other infected materials sent to the bacteriological laboratories of the Boston City Hospital and the Bureau of Laboratories of Syracuse, New York. The latter were obtained through the courtesy of Dr. Harry A. Feldman in

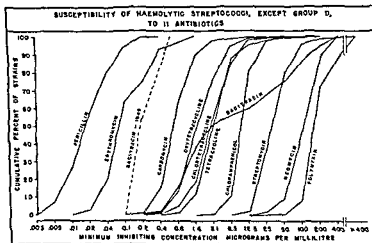


Fig 2. The 394 strains of nongroup D hemolytic streptococci upon which each of these curves is based were isolated from December 1933 through March, 1955 Included also is a curve representing the results of tests with bacitracin carried out on 25 strains of group A streptococci isolated and tested in 1949 (------)

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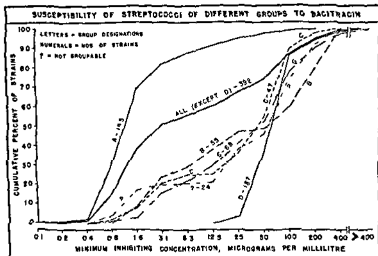


Fig 3

which then becomes more gradual This indicates that about 70 percent of the strains represented in this curve were inhibited by a relatively narrow range of concentrations—between 0.4 and 1 6 micrograms per ml.—but the remaining strains varied more widely within the higher range of concentrations, some requiring 50 microgm. per ml. (about 2.5 units) or more of bacitracin to inhibit them.

The curves representing the bacitracin susceptibility of the strains of the remaining streptococcal groups included in this study are quite similar to one another; they are more irregular in shape and spread over a wider range of concentractions than is the curve for the group A strains, and only a very small portion of them is in the range from 1.6 microgm. per ml. or less. The shape of these curves suggests a double slope, one rise in a susceptible range and another in a somewhat more resistant range, with a flatter connecting portion.

In Figure 2 it is also seen that the major portions of the curves representing penicillin and erythromycin spread over a somewhat greater range of concentrations than do the others except that of bacitracin. The contribution made by the strains of the various

whose laboratory the grouping and typing of the strains were carried out.

Most of the curves in Figure 2 have rather steep slopes with only small deviations at the extremes, each thus representing a normal distribution with a narrow spead between the concentrations required to inhibit the most sensitive and the least sensitive strains. Bacitracin is the outstanding exception; the shape of this curve is irregular and the slope more gradual, reflecting a much wider variation in the degree of susceptibility of different strains as well as an abnormal distribution curve.

From Figure 2 it can be seen that the order of activity of the different antibiotics, excluding bacitracin, against the recently isolated strains of non-group D haemolytic streptococci was as follows: 1. penicillin, 2. erythromycin, 3. carbomycin, 4. oxytetracycline, 5. and 6. chlortetracycline and tetracycline, 7. chloramphenicol, 8. streptomycin, 9. neomycin, and 10. polymyxin The relative position of chlortetracycline in this order may acutually be higher than indicated because of the more rapid deterioration of that antibiotic as compared with the others during the 48 hours incubation as employed in these tests (Love et al., 1954). The position of bacitracin in this list varies between that of oxytetracycline and that of streptomycin, depending on whether the more sensitive or the more resistant position of the bacitracin curve is being considered.

Figure 2 also shows a curve that represents the sensitivity of 24 strains of Group A strepctococci tested with bactitracin in 1949. This curve is a steep one reflecting a highly uniform susceptibility of those strains and it also falls entirely to the left of the bacitracin curve for all the recent non-group D strains. The latter fact may be due, in part, to the loss of some of the activity of the bacitracin during prolonged storage and possibly to other factors not related to differences in the resistance of the strains since there was a 4-fold difference in the bacitracin sensitivity of the standard streptococcus test strain used as a control over these years.

The resolution of the bacitracin curve of the recent strains into the component parts contributed by strains of each of the specific groups is shown in Figure 3. The curve representing the group A strains in this figure has a major portion that has a steep slope

shown in the lower panel of Figure 4; they show that group A strains were the most susceptible and group B strains the least susceptible except for the group D strains; the curves for the strains of groups C and G and the nongroupable ones occupied intermediate positions. The curves of the group D strains shown in both panels of Figure 4 reflect the considerably greater resistance of these strains to both erythromycin and penicillin as compared with those of the other groups. It is of interest, however, that, whereas the non-group D strains are more susceptible to penicillin than they are to erythromycin, the reverse is true with respect to the group D strains, the latter are more susceptible to erythromycin than to penicillin.

A comparison of the results of these tests with those obtained with 6 of the same antibiotics isolated and tested in 1949 or earlier is shown in Table 1 (p. 128). These data suggest that the recent group A strains may be slightly less susceptible than the earlier ones to penicillin, chlortetracycline, chloramphenicol and bacitracin. The susceptibility to streptomycin and polymyxin B was the same in the two studies. The decreased susceptibility to bacitracin may have been related at least in part, to deterioration of the antibiotic used, but this was not true of the other 3 antibiotics. On the other hand, the earlier data were obtained by both the broth-dilution techniques and by an agar streak-plate dilution method whereas all of the recent strains were tested by the latter method only. This method gives values for minimum inhibiting concentrations that are 2 to 4-fold greater than those obtainable simultaneously with the broth dilution method, (Jackson & Finland, 1951)

The different streptococcal groups other than D appeared to be remarkably similar in their susceptibility to the individual antibiotics, bacitracin being the outstanding exception. The latter antibiotic differentiated the group A strains which were inhibited by 3.1 microgm. (approximately 1/6 unit) of bacitracin per ml., whereas only one-fourth or fewer of the strains of other groups were inhibited by these concentrations. This difference has been exploited by Maxted (1956) who suggested the use of paper discs incorporating 5 units of bacitracin with cultures on the surface of blood agar plates to differentiate group A strains of haemolytic streptococci fro[illegible] of o[illegible] [illegible] this method, Maxted

streptococcal groups to each of these curves is represented in Figure 4 which also includes, for comparison, the curves for the susceptibility of the recent group D strains to the same antibiotics

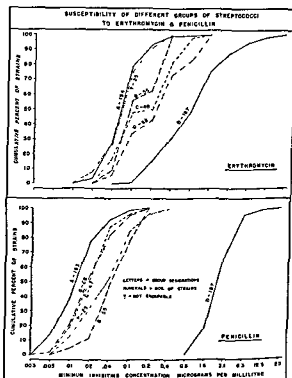


Fig 4

The upper set of curves in this figure reflects a more or less uniform distribution of the erythromycin sensitivities of the group A strains and an almost identical curve for the 25 nongroupable strains. The curves respresenting the strains of groups B, C and G, on the other hand, fall to the right of the group A curve and each has a double rise with a flatter intermediate portion; these also resemble the curves for the susceptibility of the various species of enterococcus to the tetracyclines and streptomycin and of the recent hospital staphylococci to penicillin and the tetracyclines.

The penicillin curves for the different streptococcal groups are

shown in the lower panel of Figure 4; they show that group A strains were the most susceptible and group B strains the least susceptible except for the group D strains, the curves for the strains of groups C and G and the nongroupable ones occupied intermediate positions The curves of the group D strains shown in both panels of Figure 4 reflect the considerably greater resistance of these strains to both erythromycin and penicillin as compared with those of the other groups. It is of interest, however, that, whereas the non-group D strains are more susceptible to penicillin than they are to erythromycin, the reverse is true with respect to the group D strains, the latter are more susceptible to erythromycin than to penicillin.

A comparison of the results of these tests with those obtained with 6 of the same antibiotics isolated and tested in 1949 or earlier is shown in Table 1 (p. 128). These data suggest that the recent group A strains may be slightly less susceptible than the earlier ones to penicillin, chlortetracycline, chloramphenicol and bacitracin. The susceptibility to streptomycin and polymyxin B was the same in the two studies The decreased susceptibility to bacitracin may have been related at least in part, to deterioration of the antibiotic used, but this was not true of the other 3 antibiotics. On the other hand, the earlier data were obtained by both the broth-dilution techniques and by an agar streak-plate dilution method whereas all of the recent strains were tested by the latter method only. This method gives values for minimum inhibiting concentrations that are 2 to 4-fold greater than those obtainable simultaneously with the broth dilution method, (Jackson & Finland, 1951).

The different streptococcal groups other than D appeared to be remarkably similar in their susceptibility to the individual antibiotics, bacitracin being the outstanding exception. The latter antibiotic differentiated the group A strains which were inhibited by 3.1 microgm. (approximately 1/6 unit) of bacitracin per ml, whereas only one-fourth or fewer of the strains of other groups were inhibited by these concentrations. This difference has been exploited by Maxted (1956) who suggested the use of paper discs incorporating 5 units of bacitracin with cultures on the surface of blood agar plates to differentiate group A strains of haemolytic streptococci from those of other groups. By this method, Maxted

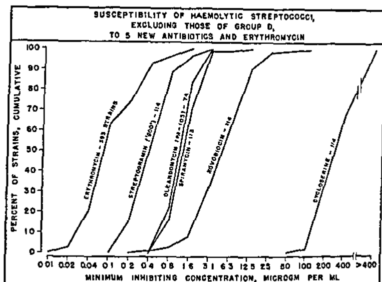


Fig 5

found that the growth of all 22 (0.9%) of 2367 group A strains was inhibited by the bacitracin in the discs, whereas only 41 (4.7%) of 840 strains of other groups were similarly inhibited. This method was also employed successfully be Levinson and Frank (1955) who found 1 unit of bacitracin to be more satisfactory for this purpose. This amount of bacitracin, in our hands, inhibited nearly all group A strains and only about 7 percent of those of other groups. Absolute quantitative comparisons of the amounts required to inhibit in the plate dilution and in the paper-disc method are not possible; however, in our study the distinction between group A strains and those of other groups would not be as sharp as indicated by the other two studies mentioned.

Erythromycin and penicillin in our study also showed suggestive differences in activity against the different streptococcal groups, those of group B being the least sensitive of those tested. The lower susceptibility of group B to penicillin had already been observed by Gezon et al., (1953). These differences, however, were not nearly so striking as that observed between the group D strains and those of all the other groups.

STREPTOCOCCUS VIRIDANS

The viridans streptococci have not been included in the present study. One of the more significant reports bearing on the possible changes in susceptibility of strains of *Streptococcus viridans* deals with the penicillin sensitivity of strains from cases of subacute bacterial endocarditis isolated at the New York Hospital during the 10 year [illegible]

alpha streptococci from patients with bacterial endocarditis.

TABLE 2.

Susceptibility of Alpha Haemolytic Streptococci from Patients with Subacute Bacterial Endocarditis

(Data from New York Hospital reported by C. A. Bernsten Jr. 1955)

Year	Number of Patients	Minimum inhibiting concentration, microgm of penicillin per ml	
		Average	Range
1944	5	0 04	0 01-0 40
1945	15	0 07	0 02-0 10
1946	17	0 07	0 02-0 17
1947	9	0 10	0 04-0 17
1948	13	0 06	0 02-0 16
1949	11	0 11	0 02-0.31
1950	8	0 12	0 05-0 16
1951	8	0 13	0 05-0 40
1952	11	0 14	0 05-0 40
1953	8	0 07	0 02-0 20

Another evaluation of the effect of penicillin usage on the susceptibility of viridans streptococci was reported by Zander (1954) who analyzed the results of three studies (Lind & Zander 1951, Welch et al., 1952, Hill et all., 1953) on the effects of long continued use of penicillin in a dentifrice In all three studies, the distribution of penicillin sensitivity of streptococci indicated that the groups using penicillin dentifrices had more organisms resistant to higher concentrations of penicillin as compared with the controls who had not been using penicillin dentifrices. Yet in all three series there were organisms in the control groups that were resistant to the same

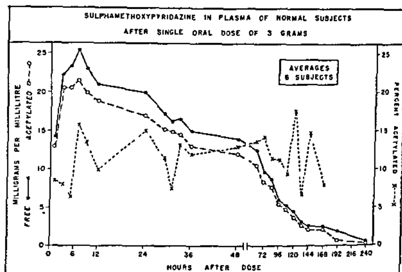


Fig. 6.

degree as some of those from treated patients. Only the proportions of the more sensitive and more resistant strains varied but within the normal range of susceptibility. Strains of high resistance that could be interpreted as the result of acquired tolerance to penicillin were not encountered.

Although there are a number of other studies suggesting that streptococci of the viridans variety have increased in resistance to various antibiotics including penicillin, none has adequate data for identification of the strains, except with regard to their haemolytic properties. It is not possible, therefore, to correlate susceptibility with species differences within the viridans group of streptococci.

A. New Long-Acting Antibacterial Sulphonamide

The role of the sulphonamides in the treatment and prophylaxis of streptococcal infections has been discussed by Mozziconacci and Labesse at this seminar (see p.) and it would appear that there is still some place for these drugs in prophylaxis, even though they may be less desirable than penicillin for that purpose and are definitely inferior in the treatment of active streptococcal infections or for the elimination of carrier organisms. Moreover, in a recent

study of the susceptibility of group A streptococci to sulphadiazine, only 1 strain out of 477 that had recently been isolated, was not inhibited by 5 mg. per 100 ml. of the sulphonamide. The distribution of types among these strains is shown in Table 3 (p. 130). It is of interest that type 17 strains were not encountered but those of type 19 accounted for 8.2 percent of the total that were tested. These two types were implicated in the sulphonamide resistant infections in American military installations referred to earlier. It is noteworthy that none of the current type 19 strains were found to be resistant to sulphadiazine. The discovery of a new sulphonamide, sulphamethoxypyridazine (Kynex) that is as active as sulphadiazine but produces and maintains higher levels in the blood is therefore of interest.

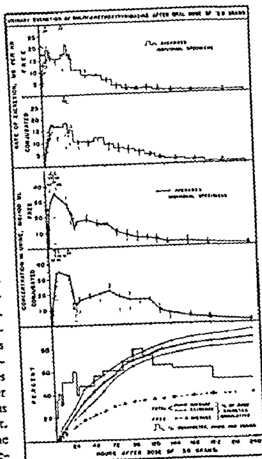


Fig 7

Fig. 6 shows the levels of sulphamethoxypyridazine in the plasma of 6 normal adult men after a single oral dose of 3 gm. of this sulphonamide. The drug was well absorbed, yielding high levels of free drug and only small amounts in the acetylated form. As

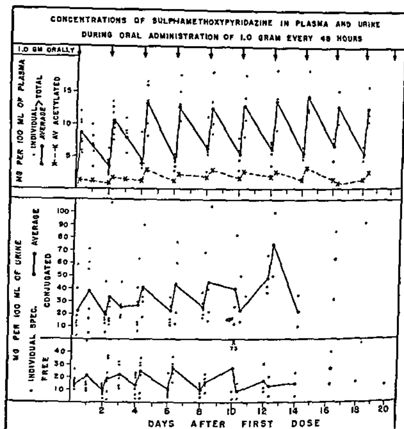


Fig 8

shown in fig. 7, the drug is cleared slowly from the plasma, the acetylated form being cleared at least 11 times as fast as the free drug. The drug in its acetylated form is adequately soluble in urine into which it is excreted; about one-half of it is in the conjugated form. Significant levels were still found in the blood after 7 days following a single oral dose of 3 gm. In a study of 7 patients on doses of 1 gm. every 48 hours (fig 8) adequate levels ranging from 5 to 12 mg per 100 ml. of plasma were maintained. Some studies are being carried out in other clinics on the potential use of this agent in the prophylaxis of streptococcal infections but it is still too soon to tell whether it will prove useful. The high blood levels

that are so readily sustained with [illegible]
doses sugg[illegible]
No to [illegible] [illegible]
headac [illegible]

Summary and Conclusions

The problems posed by the continuous administration of antibiotics have been outlined. The present status of the susceptibility of streptococci has been presented largely from the point of view of results of tests carried out at the Boston City Hospital. From these data it would appear that no significant increase in the degree of resistance of any of the beta-haemolytic or viridans streptococci has occurred in recent years.

Preliminary observations are presented on a new antibacterial sulphonamide, sulphamethoxypyridazine (Kynex) that has good antibacterial action and produces long sustained high levels in the blood from small doses. This may have potential usefulness in the prophylaxis of haemolytic streptococcal infections.

Acknowledgements:

The original studies reported in this paper were supported by a grant from the National Institutes of Health, United States Public Health Service, Department of Health, Education and Welfare. Much of this work was carried out in collaboration with Dr. Wildred F. Jones, Jr. Technical assistance by Clare W. Reed and Ann Najarian is gratefully acknowledged.

TABLE 1. *In vitro susceptibility of haemolytic streptococci,* [illegible]

Antibiotic	Series[1])	No. of Strains	Minimum Inhibiting [illegible]									
			0 003	0 005	0 01	0 02	0 04	0 1	0.2	0.4	0.8	1.6
								Per	cent	of	Strains	
Penicillin	I, all	230	1 7	19 1	64.3	13 5	1.3	0	0	0		
	A	25	0	8 0	88 0	4 0	0	0	0	0		
	II, all	391	0	6 9	19 4	30 7	23.3	13 6	5 9	0.3		
	A	193	0	13 5	25.4	38 3	15 0	6 2	1 6	0		
Erythromycin	II, A	194				3 6	25.3	50 0	14 9	1.7	0	0.5
	B	55				0	9 0	47 0	6 0	38.0	0	0
	C	48				0	15 0	31 0	2.0	13.0	17.0	2.0
	G	68				0	6 0	28 0	9 0	38.0	9.0	18.0
	?	25				8	20 0	48 0	16 0	8.0	0	0
	all	393				2 3	18 1	43 0	11.2	18.3	3.6	3 6
Carbomycin	II, all	201							0.5	14.4	47.8	27 4
	A	69							0	12.0	62.0	12.0
Bacitracin	I, A	24							54 0	46.0	0	0
	II, A	195							0 5	1.5	27.2	40 0
	B	55							0	0	0	9.0
	C	47							0	0	2.0	6 0
	G	68							0	0	3.0	2.0
	?	24							0	0	4.0	13.0
	all	392							0.3	0.8	14.3	23 0
Chlortetracycline	I, all	64					9.	52	20	11.0	6 0	2.0
	A	25					0	0	0	8.0	84.0	8 0
	II, all	393					0	0	0.3	1.0	4 1	14 2
	A	195					0	0	0	2.0	7 7	18.5
Oxytetracycline	II, all	392							0.3	0.8	12.2	34 4
	A	194							0.5	1.5	15.3	36 1
Tetracycline	II, all	394									13	[illegible]
	A	195									15	[illegible]
Chloramphenicol	I, A	25										24
	II, A	194										0
	all	394										0
Streptomycin	I, all	37										
	A	24										
	II, all	393										
	A	194										
Neomycin	II, all	393										
	A	194										
Polymyxin B	I A	24										
	II, all	392										
	A	194										

1) I includes strains isolated and tested in 1949 or earlier; II is present series, letters

other than those of group D, to 11 antibiotics.

Concentration, Micrograms per ml											
0.4	0.8	1.6	3.1	6.3	12.5	25	50	100	200	400	>400
of	*Strains*										
0											
0											
0.3											
0											
57	0	05									
380	0	0									
330	170	20									
330	90	180									
80	0	0									
18.3	36	36									
144	47.8	274	80	05	10	05					
130	620	120	130	0	0	0					
460	0	0	0	0	0	0	0	0	0	0	0
15	27.2	400	128	56	36	36	31	15	05	0	0
0	0	90	150	50	90	90	20	110	200	200	0
0	2.0	60	130	40	0	110	190	340	90	20	0
0	10	10	130	60	70	120	120	250	12.0	90	10
0	40	130	40	0	0	170	80	250	210	80	0
08	14.3	230	12.5	51	4.3	74	66	128	77	51	03
110	60	20	0	0	0	0	0	0	0		
80	640	80	0	0	0	0	0	0	0		
10	41	14.2	359	295	137	08	0.3	0	0.3		
20	77	185	431	267	20	0	0	0	0		
0.8	12.2	344	291	184	36	08	03	0	03		
1.5	355	361	309	155	0	0	0	0	0		
	1.3	109	368	391	74	30	08	05	0.3		
	15	103	456	364	61	0	0	0	0		
		240	480	200	80	0	0	0			
		0	10	12.9	608	216	31	05			
		0	05	10.5	701	169	2.3	03			
				30	30	220	590	130	0	0	0
				0	40	130	830	0	0	0	0
				03	18	351	436	155	2.9	05	05
				0	31	479	407	62	2.1	0	0
						2.0	76	377	42.0	107	
						36	88	412	40.2	6.2	
						0	0	0	71	29	0
						0.3	0.3	79	64.3	158	115
						0	0	77	75.3	144	2.6

denote streptococcal group ? = Not groupable with available antisera.

TABLE 3.

Serological types of 477 strains of group A streptococci tested for susceptibility to sulphadiazine[1])

Type	Number of Strains	% of Strains	Type	Number of Strains	% of Strains
1	78	16.4	14	8	1 7
2	10	2.1	18	4	0 8
3	35	7 3	19	39	8.2
4	29	6 1	25	18	3.7
5	4	0 8	28	3	0 6
6	95	19 9	41	2	0 4
11	1	0 2	43	4	0 8
12	27	5.7	N T.[2])	120	25.2

[1]) The tests were carried out by Dr. Harry A. Feldman, Department of Preventive Medicine, University of the State of New York, Syracuse, N.Y.; the strains were isolated in the bacteriological laboratories of the Boston City Hospital and the City of Syracuse. The tests were done in Wilson's [illegible] 5 and 25 mg. sulphadiazine per 100 ml. Only [illegible]

5 mg. per 100 ml.

[2]) N.T = not typable with available antisera.

REFERENCES

[illegible] Amer J Hyg 57 [illegible]

HILL, T J, RASCH, C and WOLLPERT, B (1953) The development of organisms with penicillin resistance associated with the use of a penicillin dentifrice. J. Dent. Res 32 453

[illegible] (1951) Comparison of methods for determining [illegible] [illegible]cterial [illegible]

[illegible]st. &

KOHN, K H, MILZER, A and MACLEAN, H (1953) Prophylaxis of recurrences of rheumatic fever with penicillin given orally final report of a five year study J Amer Med. Ass 151 347
LEVINSON, M L and FRANK, P F (1955) Differentiation of group A from other beta hemolytic streptococci with bacitracin J Bact 69 284
LIND, H E. and ZANDER, H A (1951) Penicillin resistance of streptococci and staphylococci in a penicillin dentrifice study J Dent Res 30 112
LOVE, B D, JR, WRIGHT, S S, PURCELL, E M, MOU, T W and FINLAND, M (1954) Antibacterial action of tetracycline comparisons with oxytetracycline and chlortetracycline Proc. Soc Exper Biol. (N Y) 85 25
LUND, E (1952) Determination of the sensitivity of bacteria to Aureomycin, Chloromycetin and Terramycin Acta path microbiol Scand 31 281
LUTZ, A and TROUSSEL, A (1951) Sur le degré de sensibilite ou de resistance *in vitro* de souches de streptocoques humaines et d'enterocoques a six antibiotiques (penicillin, streptomycin, chloramphenicol, aureomycin, terramycin et neomycin) Strasbourg Med 2 55-62
MAXTED, W. R (1953) The use of bacitracin for identifying group A hemolytic streptococci J Clin. Path 6 224
MILZER, A, KOHN, K H and MACLEAN, H (1948) Oral prophylaxis of rheumatic fever with penicillin. Resistant hemolytic streptococci J Amer Med Ass 136 536
POTEE, K G, WRIGHT, S S and FINLAND, M (1954) *In vitro* susceptibility of recently isolated strains of Proteus to ten antibiotics J Lab Clin Med 44 463
RANTZ, L A and RANTZ, H H (1956) Sensitivity of various clinically important bacteria to seven antibiotics Arch Intern Med 97 694
RESSELER, J and BRUYNOGHE, G (1952) Résultats des tests de sensibilité aux antibiotiques Rev Belge path 22 215
WEIL, A J and HARRIS, L (1953) Testing for antibiotic sensitivity in a general hospital Ann Intern Med 38 1027
WEIL, A J and STEMPEL, B (1953) Further studies on the antibiotic sensitivity of microorganisms isolated in a general hospital Antibiot and Chemother 3 1135
WEIL, A J and STEMPEL, B (1955) Resistance to antibiotics among the microorganisms isolated in a general hospital in 1953 and 1954 Antibiot Med 1 319
WELCH, H, RANDALL, W A, PUTNAM, L E and HENDRIKS, F D (1952) The effect of prolonged use of penicillin tooth powder on the penicillin resistance of oral microorganisms Antibiot and Chemother 2 249.
ZANDER, H A (1954) Antibiotics in dentifrices J Amer Dent Ass 48 3

COMMUNICATIONS

SOME METABOLIC AND ANTIGENIC STUDIES ON PENICILLIN-SENSITIVE AND -RESISTANT GROUP A STREPTOCOCCI

by

V. FABER

Penicillin-sensitive strains group A representative of all forty types of group A haemolytic streptococci produce the enzyme hyalurodinase, *in vitro*. This is in accordance with the high incidence of elevated titres of specific antihyaluronidase in the sera of patients

suffering from acute rheumatic fever. Most of the types produce hyaluronic acid. Addition of penicillin to the medium alters the production of hyaluronic acid as well as the production of hyaluronidase.

Penicillin-resistant strains show: morphologic changes, partial loss of gram-positive staining, loss of type-specificity, keeping of group antigen, loss of mouse-virulence, no change of haemolysin-production, loss of proteinase-production, no penicillinaseproduction, very slow growth, and partial penicillin-dependent growth. Passages in mice of these penicillin resistant strains result in variants which are still resistant to penicillin, but which have regained M-antigen and mouse virulence.

R. E. O. Williams stressed the need to search for similar resistant organisms in patients. Dr. Faber's findings gained added significance from the recent observation by Lowbury of tetracycline resistance in group A streptococci from patients with burns.

D. D. Rutstein pointed out that so far it had not been possible to isolate penicillin resistant group A streptococci from patients or carriers. Their *in vitro* demonstration by Dr. Faber was of vital interest and demanded confirmation in other laboratories. It still remained to be seen whether the phenomenon could be reproduced under natural conditions. Meanwhile it seemed reasonable to suppose that penicillin resistant strains of group A streptococci did not occur naturally or were so rare as to be of no practical importance.

DISCUSSION

B. Perry asked whether benzathine penicillin was stable in aqueous solution and whether it could have any ill effects.

M. Finland replied that this compound remained stable well beyond the expiry date given. Even if its use did not result in a violent reaction, sensitisation could occur and was sometimes prolonged.

P. Carlo pointed out that the reactions following the injection of certain batches of benzathine penicillin of English manufacture were due to impurities. When these batches were withdrawn such reactions need no longer be feared.

J. Chevallier while admitting that the efficiency of penicillin in the prophylaxis of acute rheumatic fever had been clearly demonstrated, had reservations as to the efficiency of benzathine penicillin. These were based on a particularly flagrant failure seen recently, where a severe rheumatic attack had followed a sore throat in spite of treatment with 2,400,000 units of

benzathine penicillin intramuscularly. The treatment had been instituted originally after an attack five months previously and had been regularly kept up. This was the only definite failure out of a hundred cases but possibly more would have been recorded if full therapeutic doses of penicillin had not been given before a sore throat, occurring during prophylaxis, could develop fully. It was possible that the efficacy of continuous prophylaxis with benzathine penicillin had been overestimated because failures were masked by the immediate administration of penicillin in high dosage whenever the slightest signs of infection became manifest.

P. Hedlund asked what the value was of skin tests with penicillin.

M. Finland replied that opinions still differed on this subject. Severe sensitivity reactions occurred in individuals with negative skin tests while on the other hand a patient could have a positive test and no clinical reaction.

E. G. L. Bywaters wished to know the results given by sulphonamides.

M. Finland indicated that during the last war continuous sulphonamide prophylaxis had been given to some hundreds of thousands of individuals with 18 recorded deaths. More complications, the most serous being agranulocytosis, must be expected with sulphonamides than with penicillin. Nevertheless recent figures showed that prevention by sulphonamides was efficient. Sulphonamide resistant streptococci did exist but were extremely rare. Disc methods could not be used for their detection *in vitro*.

PREVENTION OF RECURRENCES OF RHEUMATIC FEVER

by

P. Mozziconacci and J. Labesse

There are two methods of prophylaxis of recurrent attacks of rheumatic fever. The first, continuous prophylaxis, is based on the power of sulphonamides and antibiotics when administered regularly, to prevent the establishment of haemolytic streptococci in the throat. The extensive literature on this subject is summarized below. The second method of prophylaxis is the treatment of intercurrent streptococcal infections. When, in spite of continuous prophylaxis a streptococcal infection occurs, it is still possible to prevent an attack of rheumatic fever by effectively treating the sore throat. There are few figures available concerning this second method, so that on the whole the value of the various drugs used is best assessed by evaluating their ability to eradicate streptococci. On this point there are the valuable statistical studies of Rammel-

kamp and his colleagues, which, though based on young adults protected from rheumatic fever, still furnish information applicable to rheumatic children.

EFFECTIVENESS OF VARIOUS REGIMENS

1. Sulphonamides

The effectiveness of sulphonamides in preventing recurrence of rheumatic fever has been known since 1939 (Coburn and Moore, 1939; Thomas et al., 1939, 1941) and has been frequently confirmed. The data from 12 studies have been summarized by Rammelkamp (1952) (see Table 1.).

TABLE 1.

Rheumatic Recurrences after Continuous Prophylaxis with Sulphonamides (collected data).

Convalescent from rheumatic fever	Patient Seasons	Rheumatic fever recurrences (per year)	Reduction
Control	1,697	14%	86%
Sulphonamide prophylaxis	1,358	1 9%	

There are no comparable figures for prophylaxis by the treatment of intercurrent streptococcal infections with sulphonamides. On the other hand, sulphonamides have been shown to be incapable of eradicating streptococci (Morris et al, 1956, Table 2.).

TABLE 2.

Treatment of Streptococcal Infections with Sulphonamides.

	No of patients	% of subjects carrying haemolytic streptococci (of same type) during convalescence				Reduction
		9th day	13th day	21st day	35th day	
Control	253	88	85	71	46	0
Treated with sulphonamides	249	66	82	75	48	

It may be concluded that continuous chemoprophylaxis with sulphonamides is satisfactory: treatment of streptococcal infections is not, since sulphonamides are not bactericidal.

2. Oral Penicillin

The effectiveness of continuous prophylaxis with *oral* penicillin in preventing rheumatic recurrences has been shown in numerous studies (Hofer, 1949; Brick, 1950; Evans, 1950; Khon et al. 1950, 1953; Malner, 1950, Massell, 1951; Smith et al., 1952; Roberts, 1953). They have been summarized by Stollerman (1954), and although they vary both in dose employed and in method of administration their aggregate value is undoubted, (Table 3).

TABLE 3.

Continuous prophylaxis with penicillin (collected data)

Convalescents from rheumatic fever	Patient seasons	Rheumatic fever recurrences	Reduction
Control	932	8.7%	93%
Prophylactic group (penicillin)	740	0.6%	

Our results are of the same order (Table 4).

TABLE 4.

Continuous prophylaxis with penicillin (authors)

Penicillin dosage	No. of patient years	Rheumatic fever recurrences	Recurrences while on regular prophylaxis
200,000 units/day	154	3.9%	1.3%
400,000 units/day	73	2.7%	0

Massell and his colleagues (1951) have made a special study of prophylaxis by parenteral penicillin treatment of streptococcal infections (Table 5).

TABLE 5.

Rheumatic recurrences after treatment of streptococcal infections with penicillin

Convalescents from rheumatic fever	No of patients	No. of recurrences	%	Reduction
Controls	11	6	54%	85%
Treated	25	2	8%	

We have obtained analogous results (Table 6).

TABLE 6.

Rheumatic recurrences after treatment of streptococcal infections with penicillin (authors)

Convalescents from rheumatic fever	No of patients	No. of recurrences	%	Reduction
Sore throats not treated	53	31	58%	74%
Sore throats treated	19	3	15%	

The ability of oral penicillin to eradicate haemolytic streptococci has been demonstrated by Chancey et al. (1955) in young adults (Table 7).

TABLE 7.

Treatment of streptococcal infections with oral penicillin.

Number of patients	% of carriers of haemolytic streptococci during convalescence
71	2.8

Oral penicillin, therefore, is both an excellent method of continuous prophylaxis and an effective treatment of streptococcal infections.

3. Penicillin in oil with aluminium monostearate

Penicillin in oil with aluminium monostearate is as effective as oral penicillin in the prophylaxis of rheumatic fever and in the treatment of streptococcal infections.

The ability of this type of penicillin to eradicate haemolytic streptococci has been studied by Wannamaker and others (1951), Table 8.

TABLE 8.
Treatment of streptococcal infections with penicillin aluminium monostearate.

	No of patients	% of carriers of haemolytic streptococci of the same type during convalescence	Reduction
Controls	422	34.6%	80%
Treated group	426	6.8%	

The best results were obtained (Wannamaket, 1954) by 4 injections of 600,000 units given at intervals of 48 hours. It is likely that this treatment could be reduced to 3 injections.

4. Benzathine penicillin G (Dibenzyl-ethylenediamine-bipenicillin G)

The use of this long-acting penicillin as a monthly infection of 1,200,000 units ensures effective continuous prophylaxis. Table 9 summarizes the results of Stollerman et al. (1954), Diehl et al. (1954), Perry and Gillespie (1954) and McCue et al. (1955).

TABLE 9.
Rheumatic recurrences after continuous prophylaxis with long-acting penicillin (collected data)

Convalescent from rheumatic fever	No of patient years	No of recurrences	%	Reduction
Controls (treated with sulphadiazine)	277	7	2.5%	92%
Benzathine penicillin group (1,200,000 units every 4 weeks)	574	1	0.17%	

Out results are comparable (Table 10).

TABLE 5.

Rheumatic recurrences after treatment of streptococcal infections with penicillin

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Convalescents from rheumatic fever	No of patients	No. of recurrences	%	Reduction
Sore throats not treated	53	31	58%	74%
Sore throats treated	19	3	15%	

The ability of oral penicillin to eradicate haemolytic streptococci has been demonstrated by Chancey et al. (1955) in young adults (Table 7).

TABLE 7.

Treatment of streptococcal infections with oral penicillin.

Number of patients	% of carriers of haemolytic streptococci during convalescence
71	2.8

Oral penicillin, therefore, is both an excellent method of continuous prophylaxis and an effective treatment of streptococcal infections.

3. Penicillin in oil with aluminium monostearate

Penicillin in oil with aluminium monostearate is as effective as oral penicillin in the prophylaxis of rheumatic fever and in the treatment of streptococcal infections.

The ability of this type of penicillin to eradicate haemolytic streptococci has been studied by Wannamaker and others (1951), Table 8.

TABLE 8.
Treatment of streptococcal infections with penicillin aluminium monostearate.

	No of patients	% of carriers of haemolytic streptococci of the same type during convalescence	Reduction
Controls	422	34 6%	80%
Treated group	426	6 8%	

The best results were obtained (Wannamaker, 1954) by 4 injections of 600,000 units given at intervals of 48 hours. It is likely that this treatment could be reduced to 3 injections.

4. Benzathine penicillin G (Dibenzyl-ethylenediamine-bipenicillin G)

The use of this long-acting penicillin as a monthly infection of 1,200,000 units ensures effective continuous prophylaxis. Table 9 summarizes the results of Stollerman et al (1954), Diehl et al. (1954), Perry and Gillespie (1954) and McCue et al. (1955).

TABLE 9
Rheumatic recurrences after continuous prophylaxis with long-acting penicillin (collected data)

Convalescent from rheumatic fever	No. of patient years	No of recurrences	%	Reduction
Controls (treated with sulphadiazine)	277	7	2 5%	92%
Benzathine penicillin group (1,200,000 units every 4 weeks)	574	1	0 17%	

Our results are comparable (Table 10).

TABLE 10

Rheumatic recurrences after continuous prophylaxis with long-acting penicillin (authors)

	No of patient years	No. of recurrences	%
1,200,000 units monthly	199	1	0 5%

There are no figures showing the prevention of recurrences by the treatment of streptococcal infections with benzathine penicillin, but Chancey (1955) has shown the ability of this preparation to eradicate streptococci (Table 11).

TABLE 11.

Treatment of streptococcal infections with long-acting penicillin

Subjects protected against rheumatic fever	No of patients	No. of carriers during convalescence
1,200,000 units/month	71	0

Injections of benzathine penicillin are therefore equal to or superior to oral penicillin.

5. Aureomycin* and terramycin*

The value of aureomycin for continuous prophylaxis has been shown by McVay and Sprunt (1953), (Table 12).

TABLE 12.

Rheumatic recurrences after continuous prophylaxis with tetracyclines.

Convalescent from rheumatic fever	No of patients	No. of recurrences	%	Reduction
Control group	12	4	33%	81%
Treated group	23	1	4.3%	

In addition, the ability to eradicate haemolytic streptococci has been studied by Houser et al. (1953) for aureomycin, and by Catanzaro et al. (1955) for terramycin, (Table 13).

* Chlortetracycline and Oxytetracycline.

TABLE 13.
Treatment of streptococcal infections with tetracyclines.

Treatment	Subjects with no history of rheumatic fever	No of patients	% of carriers during convalescence	Reduction
Aureomycin	Control group	78	70 5	52%
	Treated group	65	33 8	
Terramycin	Control group	473	53	55%
	Treated group	300	24	

The effectiveness of the broad spectrum antibiotics is therefore real, but inferior to that of penicillin.

COMPLICATIONS

Toxic reactions from sulphonamides

The incidence of toxic and sensitivity reactions after continuous sulphonamide prophylaxis has varied considerably in different studies. Stollerman et al. (1954) reported 0.5% of rashes and 0 01% of blood dyscrasias, wheread Denny (1954) found that sulphonamides had to be discontinued in 10% of cases because of various untoward reactions. Stowell and Button (1941) reported one death, while we have had one fatal case of Stevens-Johnson syndrome.

Sensitivity reactions to penicillin

Chancey et al. (1955) have recorded various kinds of sensitivity reaction in young adults following the different regimes of penicillin prophylaxis (Table 14).

TABLE 14.
Sensitivity reactions after prolonged penicillin prophylaxis

	1,200,000 Benz P	600,000 Benz P	500,000 oral Penicillin	Placebo
Angioneurotic oedema	4 06%	1 47%	0 85%	0 7%
Joint symptoms	1 15%	0 63%	0 24%	2%
Rashes	1 15%	1 16%	1.30	3%

It will be noted that allergic reactions are more frequent following 1,200,000 units of benzathine penicillin than after 600,000 units, or after oral penicillin.

We have had only one case of sensitisation in children. It was limited to the appearance of urticaria and did not interfere with treatment.

Changes in the drug sensitivity of the pharyngeal flora during prolonged chemoprophylaxis are summarized in Table 15.

TABLE 15.

Changes in drug-sensitivity during prolonged chemo-prophylaxis

Haemolytic streptococci Group A	*None penicillin resistant: some acquire resistance to sulphonamides*
Strep viridans	Numbers not increased (Miller & Massell 1956) Sensitivity to penicillin: 0 01-0 5 units (Stollerman, 1952) 0 01-1 0 units (Krumwiede, 1949)
Gram negative organisms	Proportionately increased. No clinical manifestations (Miller and Massell)
Staphylococci	*Frequently penicillin resistant*

We have frequently observed the development of staphylococcal infections in subjects during penicillin prophylaxis. Though persistent in hospital, these infections subside readily at home.

Continuous chemoprophylaxis with penicillin does not therefore involve any serious danger due to modifications of the pharyngeal flora in the course of prolonged treatment.

COMPARISON OF THE DIFFERENT METHODS

A comparison of the relative advantages and disadvantages of prophylaxis or treatment of streptococcal infections with sulphonamides and antibiotics is set out in Table 16.

TABLE 16.

Comparison of sulphonamides and antibiotics

	Advantages	Disad-vantages	Complica-tions	Efficiency	
				Contin prophyl	Treatment of Strep infections
Sulphon-amides	Cheap	Not bactericidal Development of resistant streptococci	Rashes 0 5% Blood disorders 0 01%	86%	0
Penicillin	Bactericidal Never any resistant organisms	More expensive (Least for benzathine penicillin injections)	Sensitivity reactions	93-100%	90-100%
Aureomycin Terramycin	Bactericidal-bacteriostatic	Expensive Possibly resistant organisms	Intestinal upsets Fungal infections	81%	60-80%

Continuous prophylaxis is best provided by penicillin, but if this is not possible, by sulphonamides, or lastly, aureomycin

Treatment of streptococcal infections is best carried out with penicillin, or if this is not possible, with aureomycin or terramycin, but never with sulphonamides.

A comparison of oral penicillin with injections of benzathine penicillin is set out in Table 17.

TABLE 17.
Oral v. long-acting parenteral penicillin

	Advantages	Disad-vantages	Complica-tions	Efficiency	
				Contin prophyl	Treatment of Strep infections
Oral penicillin	Ease of ad-ministration Adequate amounts obtained regularly	Continuity not certain More expensive	Allergic reactions rare (0 3-0 7%)	93%	90-100%
Benzathine penicillin injections (1,200,000 units)	Continuity certain Cheap	Needs injections Adequate level not certain	Allergic reactions more frequent (4 06%)	100%	90-100%

The chief advantage of intramuscular benzathine penicillin is that it ensures continuity of treatment Its chief drawbacks are that an adequate blood level of penicillin is not certain and that allergic reactions are frequent. In practice, the effectiveness of this method has been shown by its excellent results clinically, while sensitivity reactions have been rare in children.

METHODS OF ADMINISTRATION OF CHEMOTHERAPY

The dosage of the different drugs for continuous prophylaxis and for treatment of intercurrent streptococcal infectons is set out in Table 18.

TABLE 18.
(a) Prophylaxis

Penicillin		Sulphadiazine
Oral penicillin	Penicillin G 200,000 units × 2 b d.	0 5-1 0 gm /day
	Penicillin V 100,000 units × 2 b d	
Benzathine penicillin injection	1,200,000 units once a month or 600,000 units twice a month	

(b) Treatment of streptococcal sore throat

Penicillin		Aureomycin Terramycin
Oral penicillin	Penicillin G 200,000 units q d s for 10 days	2 gm /day for 10 days
	Penicillin V 100,000 units q d s for 10 days	
Procaine penicillin	*3 injections of 300,000 or 600,000 units at 2 day intervals*	
Benzathine penicillin *injection*	1 injection i m of 1,200,000 units	

In regard to the duration of continuous prophylaxis, the studies of Wilson (1940) showed that the chances of a recurrence of rheumatic fever fall markedly after puberty or when five years have elapsed after the first attack. Continuous prophylaxis should be carried on for at least five years and in any case up to the age of 15 years. However, it is necessary to distinguish between cases with and without cardiac involvement when rigorously applying these rules.

As regards the treatment of intercurrent streptococcal infections, the clinical diagnosis of the streptococcal nature of a pharyngitis is based on the sore throat, dysphagia, intense redness of the pharynx with oedema and exudate, and markedly swollen glands. But a precise diagnosis is only possible in 75% of cases (Breese and Disney, 1954) and clinical diagnosis should be supported by laboratory examinations (see p. 14).

Acute sore throats in rheumatic subjects should always be regarded as being streptococcal in origin and treated vigorously with penicillin.

Other therapeutic measures

Public health measures designed to avoid and to control the spread of streptococcal infections are considered in Part IV.

Attempts at specific immunisation made by Epidemiology Unit No 22, (1946) and by Rantz et al. (1949) had no success. They failed partly because of the need to immunise each group with the

streptococcal types to which they were exposed and partly because of the severe sensitivity reactions which occurred in some cases.

The indications for or against tonsillectomy in the rheumatic subject are difficult to evaluate. Although Wilson (1940) maintained that the indications are the same as for the non-rheumatic child, there is no doubt that children with tonsillar tissue are more likely to be streptococcal carriers than children without, and it might therefore seem reasonable to remove this possible focus of infection in the highly susceptible rheumatic subject. Tonsillectomy, if and when it is done, should be accompanied by a course of penicillin treatment to avoid the risk of post-operative infection.

REFERENCES

DODGE, K G, BLADWIN, J S and WEBER, M W. (1944) The prophylactic use of sulfanilamide in children with inactive rheumatic fever. J. Pediat. 24 483

FELDT, R. H (1944) Sulfanilamide as a prophylactic measure in recurrent rheumatic infection a controlled study involving 131 "patient-seasons" Amer J Med. Sci 207 483

GLAZEBROOK, Z J and THOMSON, E (1942) Administration of Vitamin C and its effect on general health and resistance to infection J Hyg Lond. 42 1

HANSEN, A E, PLATOU, R V and DWAN, P F (1942) The prolonged use of a sulfonamide compound in the prevention of rheumatic recrudescences in children Amer J Dis Child 64 963

HOFER, J W (1949) Oral penicillin for children with rheumatic fever J Pediat 35 135

HOUSER, H B, ECKHARDT, G C, HAHN, E O, DENNY, F W, WANNAMAKER, L W and RAMMELKAMP, C H (1953) Effect of aureomycin treatment of streptococcal sore throat on the streptococcal carrier state, the immunologic response of the host, and the incidence of acute rheumatic fever Pediatrics 12 593

KOHN, K. H, MILZER, A and MCLEAN, H (1950) Oral penicillin prophylaxis of recurrences of rheumatic fever J Amer Med Ass 142 20

KOHN, K H, MILZER, A and MCLEAN, H (1953) Prophylaxis of recurrences of rheumatic fever with penicillin given orally J Amer Med Ass 151 347

KRAUMWIEDE, E (1949) Penicillin resistance of non-hemolytic streptococci from rheumatic children receiving prophylactic penicillin Pediatrics 4 634

KUTTNER, A G and REYERSBACK, G (1943) The prevention of upper respiratory infections and rheumatic recurrences in rheumatic children by the prophylactic use of sulfanilamide J Clin Invest 22 77

MCCUE, C M, GIBSON, C D, and LINDEMANN, L C (1955) A comparison of intramuscular benzathine penicillin and oral sulfonamide in the control of rheumatic recurrences J Pediat 47 450

MCVAY, L V and SPRUNT, D H (1953) Aureomycin in the prophylaxis of rheumatic fever New Eng J Med 249 387

MAILNER, M M (1950) Oral penicillin in the prophylaxis of recurrent rheumatic fever J Pediat 37 858

MAILNER, M M and AMSTERDAM, S D (1947) Oral penicillin in the prophylaxis of recurrent rheumatic fever J Pediat 31 658

MAILNER, M M, AMSTERDAM, S D and ARRECHE, C (1949) Further studies on oral penicillin in the prophylaxis of recurrent rheumatic fever J Pediat 35 145

MASSELL, B F (1951) Present status of penicillin prophylaxis of rheumatic fever Mod Concepts of Cardiov Dis 20 108

MASSELL, B F, STURGIS, G P, KNOBLOCH, J D, STREEPER, R B, HALL, T N and NORCROSS, P (1951) Prevention of rheumatic fever by prompt penicillin therapy of hemolytic streptococcal respiratory infections a progress report J Amer Med Ass 146 1469

MESSELOFF, C R and ROBBINS, M H (1943) The prophylactic use of sulfanilamide in children with rheumatic heart disease J Lab Clin Med 28 1323

MILLER, J M and MASSELL, B F (1956) Studies of bacterial throat flora during chemoprophylaxis of rheumatic fever New Eng J Med 254 149

MORRIS, A J, CHAMOVITZ, R, CATANZARO, F J and RAMMELKAMP, C H (1956) Prevention of rheumatic fever by treatment of previous streptococcic infection Effect of sulfadiazine. J Amer Med Ass 160 114

PERRY, C B, GILLESPIE, W A (1954) Intramuscular benzathine penicillin in the prophylaxis of streptococcal infection in rheumatic children. Brit Med J 2 729

RAMMELKAMP, C. H, HOUSER, H B, HAHN, E O., WANNAMAKER, L W, DENNY, F W and ECKHARDT, G. C (1952) The prevention of rheumatic fever, "Rheumatic Fever" (Thomas) University of Minneapolis, Minneasota Press

RANTZ, L A, RANDALL, E and RANTZ, H H (1949) Immunization of human beings with group A hemolytic streptococci Amer J Med 6 424

ROBERTS, E. (1953) Use of sulfonamides and penicillin to prevent recurrences of rheumatic fever, a twelve years study Am J Dis Child 85 643

[illegible]

fever Amer J Med 17 737.

STOLLERMAN, G H, RUSOFF, J H. and HIRSCHFELD, I (1955) Prophylaxis against group A streptococci in rheumatic fever New Eng J Med. *252* 787.

STOWELL D D and BUTTON, W H (1941) Observations on the prophylactic [illegible]

Ass 117 2104

THOMAS, C B and FRANCE, R (1939) A preliminary report of the prophylactic use of sulfanilamide in patients susceptible to rheumatic fever. Bull J Hopkins Hosp *64* 67

THOMAS, C B, FRANCE, R. and REICHSMAN, F (1941) The prophylactic use of sulfanilamide in patients susceptible to rheumatic fever. J Amer. Med Ass *116* 551

WANNAMAKER, L W, RAMMELKAMP, C H, DENNY, F. W., BRINK, W. R., HOU- [illegible]

COMMUNICATIONS

THE PREVENTION OF RHEUMATIC FEVER RELAPSES BY ORAL PENICILLIN

by

R. CRUICKSHANK

During a period of two years, 1946–'48, a controlled trial of the prophylactic effect of oral Penicillin G in preventing fresh streptococcal infection and rheumatic relapse was carried out in some 300 children, aged 5–13 years, admitted to a Home for patients convalescing from rheumatic fever. The penicillin was given daily in a single dose of 100,000 units in 5% glucose half an hour before breakfast to alternate cases during the six months of their residence in the Home. Besides a careful clinical assessment of cases presenting evidence of sore throat or fresh rheumatic activity, weekly nose

and throat swabs from all the children were examined for beta-haemolytic streptococci, and blood samples were tested monthly or, where indicated, more frequently for antistreptolysin O titres and erythrocyte sedimentation rate. All cultured strains of group A streptococci isolated during the two-year survey were examined for Griffith type. All remained highly sensitive to penicillin

In two very comparable groups of approximately 150 children, one given oral penicillin and the other a control group, the streptococcal carrier rate was four times higher in the controls than in the penicillin treated children. (Table 1). There were seven definite cases and two doubtful cases of streptococcal tonsillitis among the controls and only one doubtful case in the treated group (Table 2). Similarly, there were four rheumatic relapses among the controls and none among the treated children. It may be noted that only one of the rheumatic relapses was preceded by a clinical attack of streptococcal tonsillitis. Type 22, was isolated from the throats of two of the symptomless cases before the rheumatic relapse

In addition to the clinical streptococcal sore throats, there were numerous instances of subclinical streptococcal infection associated with a rise in the A.S.O. titre, and in some cases, a rise in the erythrocyte sedimentation rate. There were 9 such cases in the control group and 4 in the penicillin group. These findings illustrate some of the difficulties that would be met in trying to prevent primary rheumatic attacks following *clinical* streptococcal infection.

TABLE 1.

Incidence of Streptococcus pyogenes carriers in two groups of children. (penicillin treated and control)

	Penicillin group	Control group
Total no of patients	155	145
No of *patient-weeks in home*	3,345	3,248
Average length of stay in weeks	21 6	22 4
No of patient-weeks *Str pyogenes* carried in throat	71	242
No of patients carrying *Str pyogenes* in throat for two consecutive weeks	7	33
No of patients carrying *Str pyogenes* in throat for three consecutive weeks	4	17

TABLE 2.

Incidence of streptococcal pharyngitis in two groups of children. (penicillin treated and control).

Penicillin	Control
1 doubtful case (Group A Strep No rise in A S O)	7 definite cases with *Str. pyogenes* (Rise of A S O in 6 cases) 2 doubtful cases (No haem strep Rise of A S O)

EFFECTIVENESS OF ANTIBIOTICS AND CHEMOTHERAPEUTIC AGENTS IN THE PREVENTION OF RECURRENCES OF RHEUMATIC FEVER

by

M. AVCIN.

Our results since we introduced prophylactic treatment with oral penicillin (up to 100,000 units per day) or sulphadiazine (0.5 to 1 g) or a combination of the two, for every rheumatic fever patient leaving the Paediatric Clinic in Ljubljana serve to illustrate the effectiveness of prophylaxis. In 1954 and 1955 of 202 cases followed regularly, there were only 9 cases of recurrence in the 133 children given prophylactic treatment (6.7%), but there were 10 in the 69 cases who received no prophylactic treatment (14.4%). The question arises whether in order to prevent rheumatic disease it is advisable to have recourse to high doses of antibiotics in all upper respiratory infections. Many authors advise against the exhibition of penicillin even with a slight sore throat because they feel that the child should be given a chance of developing some immunity to group A streptococci since these bacteria are so prevalent in its surroundings.

1,094 cases observed between 1939 and 1945 = 99 recurrences
344 cases observed between 1953 and 1955 and treated with oral penicillin = no recurrences.

Analysis of the recurrences in our children made us attribute the high proportion of 6.6% to errors in applying the treatment. In fact two children, despite strict instructions, did not increase the dose of penicillin when intercurrent infections occurred. In one, recurrence followed an ordinary nasopharyngitis, in the other a simple tooth extraction. The four other children with recurrences took the penicillin with meals which meant a decrease in absorption and consequently in the penicillin blood levels reached.

RECURRENCES OF RHEUMATIC FEVER IN CHILDREN GIVEN CONTINUOUS PROPHYLACTIC PENICILLIN

by

J. CHAPTAL, R. JEAN, MME. C. CAMPO AND R. BONNET

The prevention of recurrences of rheumatic fever by continuous penicillin therapy is based on two concepts: the part played by streptococcal infections in the production of the disease and the unfailing effectiveness of penicillin against the streptococcus, a bacterium whose strains do not acquire resistance to this antibiotic. This treatment has been applied long enough for it to be possible to appreciate its effect.

We gave continuous prophylactic penicillin to 120 children convalescing from rheumatic fever. It was given by mouth in two to three doses of 400,000 to 600,000 units per day. 90 children carried out the treatment strictly, 30 gave it up early.

The proportion of recurrences was as follows there were 6 recurrences (6.6%) in the 90 cases treated properly and 8 recurrences in the 30 insufficiently treated (26%). The wide difference in the proportion of recurrences in the two groups clearly illustrates the

authors. To quote only one example, the statistics of the Good Samaritan Hospital in Boston are as follows:

THE OCCURRENCE OF BETA HAEMOLYTIC STREPTOCOCCI IN CHILDREN GIVEN CHEMOPROPHYLAXIS AND IN CONTROLS

by

M. R. H. Stoppelman

In 1948 the Paediatric Clinic of Amsterdam University opened a rheumatism unit. Discharged patients are followed up and new cases for confirmation of the diagnosis of rheumatic fever are examined.

The usual dose of continuous sulphadiazine is administered prophylactically for 5 years. Up to the present 257 children have been treated. 170 took the sulphadiazine regularly, 48 irregularly and 39 stopped taking it before the 5 years had elapsed.

Children being given prophylactic treatment are examined every month and this includes examination of the heart and a blood analysis. Pharyngeal swabs are taken and examined for haemolytic streptococci. From January, 1953 to May, 1955 we have used Holmes and Lermit's technique and medium. The swab is put in a tube containing modified Pike's medium, placed in the incubator for 24 hours, then cultured on horse blood agar and incubated anaerobically. Table 1 shows the absolute figures and the percentages of negatives and positive cultures obtained with the two methods in the three groups of children studied.

Eleven of the 125 strains of haemolytic streptococci isolated were resistant to 8 gamma/ml. sulphadiazine. H.C. Zanen (Table 2) determined the type of 50 of these strains.

In most of the cases bacteriological examination was positive on only one occasion. Children whose pharyngeal swabs were repeatedly positive were given intramuscular penicillin for 6 days. In one of these several courses of this treatment were unsuccessful in eliminating the streptococcus which was a type 24; it eventually disappeared spontaneously.

To sum up, it can be said that chemoprophylaxis with sulphonamide does not succeed in reducing to zero the incidence of haemolytic streptococcal infections However, there is a reduction in the number of positive pharyngeal swabs in treated children as

compared with controls: this difference is statistically significant.

The results of bacteriological examination depend to a large extent on the method of isolation The absence of haemolytic streptococci in a swab does not imply that the bacterium is not present inside the tonsils.

TABLE 1

Incidence of haemolytic streptococci in pharyngeal swabs.

	Regular chemoprophylaxis			*Irregular chemoprophylaxis*			*No chemo-prophylaxis*		
	negative cultures	positive cultures		negative cultures	positive cultures		negative cultures	positive cultures	
	number	number	%	number	number	%	number	number	%
culture on blood agar	2154	62	2 8	404	16	3 8	366	20	5 2
culture by Holmes & Lermit's method	918	47	4 9	173	12	6 5	216	26	12

TABLE 2.

Griffiths type distribution of haemolytic streptococci from rheumatic convalescents.

Type	*No of strains*	Type	*No of strains*
1	2	12	10
2	1	13	3
3	9	14	2
4	1	24	1
5/27/44	5	25	2
6	5	28	2
8	1	indeterminable	6

THE RISK OF STREPTOCOCCAL RE-INFECTION IN CONVALESCENT HOMES FOR RHEUMATIC CHILDREN

by

P. Chassagne and J. Chevallier

For some years the National Institute of Hygiene has been able to group together a certain number of cases of rheumatic fever with a view to their systematic study. The results of this investigation which covers several hundreds of cases have been published elsewhere.* We would just like to make two short observations.

The first concerns the incidence of acute naso-pharyngeal infections in children convalescing in special centres and in children who go straight home to their families when they leave hospital.

An acute upper respiratory tract infection occurred 38 times in 100 children almost all suffering from a rheumatic heart condition during their stay of several months in a convalescent home. In 20 cases bacteriological examination showed the presence of haemolytic streptococci in the naso-pharynx. These results must be treated with reserve because at the time that these observations were made the possibility of grouping streptococci was still slight.

There were 62 children followed at home for whom sufficiently precise information was available (the patients were seen several times in the months following their discharge from hospital). In only 8 did a nasopharyngeal infection occur during the 3 months after they left hospital. Statistical analysis shows that the difference in incidence of acute naso-pharyngeal infections in the two groups is significant.

The grouping of rheumatic fever patients in convalescent homes, so desirable from several points of view, can therefore produce *special prophylactic problems.*

A second point merits consideration: What were the consequences of these re-infections? There was a recurrence of rheumatism *in four of the children sent straight home,* but none of the children in the convalescent home suffered a relapse. It is here that we see the decisive part played by properly applied treatment: the

* J. Chevallier, Etude sur la maladie de Bouillaud, radiographie de l'I.N.H. 1956, no 9.

nosa-pharyngeal re-infection is discovered early in the child in the convalescent home and suitable treatment quickly cures it. Re-infection in the child at home, on the other hand, is often not recognised at the start and local treatment of no real value is instituted—thus was our experience.

These observations emphasize once again the importance of effective chemotherapy in the various stages of rheumatic fever. The disappearance of any risk of re-infection in the centres where it is regularly applied proves its value.

PROPHYLAXIS AGAINST INFECTION IN CHILDREN CONVALESCING FROM RHEUMATIC FEVER

by

R. CARRON

In a community of children having recently suffered an attack of rheumatic fever who were in a convalescent home in the Lyons district we tried to estimate the results of chemo-prophylaxis by studying the incidence of febrile naso-pharyngeal infections and of rheumatic recurrences requiring the re-institution of hormone treatment. We compared the figures of naso-pharyngeal infections in these children with a control group made up of children living under the same roof but suffering from diseases of the alimentary tract or kidneys who had had no prophylactic treatment.

During 1952-53 no chemo-prophylaxis was instituted unless it was prescribed by the doctor in charge. Naso-pharyngeal infections occurred in nearly all the children convalescing from rheumatic fever and there were two recurrences (see table).

In 1954, in view of the frequency of naso-pharyngeal infections, all the patients convalescing from rheumatic fever were given continuous oral prophylactic treatment consisting of either a daily tablet of benzathine penicillin (200,000 units) or alternate courses of treatment of 5 days of tablets of penicillin to suck or of sulphonamides. There was a drop in the incidence of naso-pharyngeal infections but no change in the proportion of recurrences.

In 1955 regular and uniform prophylaxis was instituted for all these children consisting of bi-monthly intramuscular injections of 600,000 units of benzathine penicillin. The decrease in the number of

naso-pharyngeal infections and especially of recurrences was very considerable.

During the first six months of 1956 this prophylaxis was systematically followed. The proportion of naso-pharyngeal infections remained the same and there was no recurrence.

between this group and that of rheumatic fever convalescents stands out all the more as a result. The reduction in the size of the control group during these years was due to the extension of prophylactic measures to patients convalescing from nephritis and even to diabetics.

Benzathine penicillin prophylaxis is now the absolute rule with us and is applied to all our convalescents. It has many advantages: it is simple to administer, there is no possibility of irregular treatment or of refusal on the part of the child as happens so often with oral administration, its cost is reasonable and, above all, it has an incontestable prophylactic value, which for the present at any rate is much superior to oral administration.

Rheumatic recurrences after various forms of chemoprophylaxis (see text)

	1952-53	*1954*	*1955*[1])	*6 months 1956*
Number of rheumatic fever convalescents	11	22	33	35
Average stay of child (In days)	135	96	109	111
Total number of convalescent children having a naso-pharyngeal infection during their stay	10 (91%)	14 (63%)	6 (18%)	6 (17%)
Total number of relapses	2 (18%)	4 (18%)	1 (3%)	0
Control group followed for the same period	101	37	17	7
Number of controls with naso-pharyngeal infection	30 (29%)	13 (29%)	7 (41%)	4 (57%)

1) Regular, and uniform chemoprophylaxis introduced.

The disadvantages are minimal: frequent pain lasting for several hours at the site of injection, a not infrequent rise in temperature (38°) 12 to 36 hours after injection, rare cases of intolerance (one case of purpura associated with arthritis). Of the acute febrile infections which occurred in 1956, 4 appeared 12 to 14 days after an injection of benzathine penicillin.

During the last few months we have taken swabs of the throats of children under prophylactic treatment whose pharyngeal mucosa appeared to us to be abnormal From 6 children examined a streptococcus viridans which had either a marked or slight resistance to penicillin was isolated on 4 occasions. Penicillin resistant staphylococci were present in every case.

DISCUSSION

A. Wallgren remarked that polyarthritis and a raised blood sedimentation rate can occur in other diseases besides rheumatic fever in which case continuous prophylactic penicillin administration was not necessary

D D Rutstein emphasized the importance of this remark. Indeed, the major symptom of polyarthritis could be combined with minor symptoms such as fever and a raised blood sedimentation rate in many other diseases besides rheumatic fever In his original communication in 1944, T D Jones raised this point and he had developed this theme in "Jones's modified criteria" (1956) *where the following appears "combinations of these* diagnostic criteria that occur in the presence of other illnesses must be ruled out before a definitive diagnosis is made" The combination of polyarthritis, fever and a raised blood sedimentation rate was then mentioned and that was the point which interested us.

P Isorni asked if the prophylactic measures which had been described could prevent the appearance of rheumatic carditis which seemed to develop independently of the acute attack and of which mitral stenosis was the most typical example

P Mozziconacci replied that prophylaxis had no effect on an established carditis and the mechanism by which mitral stenosis could occur silently silently was still unknown

[illegible]

and there would be a reduction in the cost of providing medical care for patients in the acute stage. Prevention of recurrences of rheumatic fever would reduce the number of cases of myocardial damage and consequently of aortic and mitral insufficiency On the other hand, all the data at our disposal

tended to show that the process responsible for the establishment of mitral stenosis was not related to the number or severity of attacks of rheumatic fever.

This opinion was founded on the following points·

a) The absence of clinically verified rheumatic fever in the history of almost half the cases of adult mitral stenosis.

b) Several studies did not show any correlation between the number of attacks of rheumatic fever and the development of mitral stenosis In none of the published articles was there any sign of this correlation.

c) The severity of the stenosis of the mitral orifice, as verified at autopsy, did not depend on the number of attacks which the patient had had, but was correlated with the length of time which had elapsed between the first attack of rheumatic fever and death.

d) Microscopical examination of muscle biopsies made at the time of mitral valvotomy supported the persistence of an active pathological process in the heart, even though clinical proof of rheumatic activity was entirely absent. Thus, there was no indication that the prevention of recurrences would halt the appearance of mitral stenosis in patients who had already suffered an acute attack. However, considering the other advantages of prophylaxis, it should be widely applied.

J. Labesse pointed out that recurrences during prophylaxis did not cause aggravation of the carditis. Thus, of the children who had been given prophylactic treatment at La Roche Guyon, 10 had had normal hearts before the recurrence and 11 after, that is to say, one carditis had regressed. On the other hand, of the group who had not been given prophylactic treatment, 16 had had normal hearts before the recurrence and only 6 after

R. Debré stressed the value of an establishment like La Roche Guyon where thanks to the prophylactic methods used, it had been possible to suppress streptococcal sore throats This scheme was worth copying else- [illegible] country to country,

[illegible] ds this

[illegible] socia-

[illegible] Jones'

criteria

G. Fanconi was convinced by the opinions expressed that it was our duty to intensify the penicillin prophylaxis of rheumatic fever Even the prevention of streptococcal infections in healthy persons had been envisaged. Now, this idea ran counter to everything which the speaker had hitherto taught. He had indeed always taken a stand against the abuse of antibiotics and chemotherapy for various reasons:

(a) The formation of natural antibodies should not be inhibited

(b) Destruction of the normal flora of the pharynx, and more particularly of the intestine, favoured the multiplication of antibiotic-resistant bacteria, such as the staphylococcus, Oidium albicans, etc. He had lost several babies from enterocolitis due to resistant staphylococci. He admitted that the

danger was not so great with thrush although he had seen very young children die of generalized moniliasis after treatment with several antibiotics.

(c) Antibiotics could cause allergic and even anaphylactic states.

We were therefore confronted by a dilemma which seemed insoluble

T. Jersild believed that in giving children high doses of penicillin from the first attack of rheumatic fever onwards and in pursuing this preventive treatment for several years, sometimes even until puberty, there was a risk of producing hypersensitivity the results of which could be serious, even lethal, and of causing bacterial resistance, especially of staphylococci

On the other hand, penicillin treatment should be given to every rheumatic child in whom an infection, however slight, of the pharynx, sinuses, ear or respiratory tract appeared, or if these infections occurred in the child's family or in the institution which he frequented

Oral penicillin V was advantageous for two reasons first, because no [illegible]

infections, cause a change in our attitude to penicillin?

However theoretical the objection to continuous penicillin prophylaxis might be, *D D Rutstein* had known a case where staphylococcal endarteritis had appeared in a persistent ductus arteriosus in a child who had been given penicillin prophylaxis The infection had been resistant to every treatment and the child had died Such cases should be known so that the risks could be calculated. To-day, however, it was time to say that the advantages of prophylaxis far outweighed the potential dangers of a superinfection with a penicillin-resistant stapyylococcus

P. Mozziconacci, while confirming that staphylococcal infections did occur in children under collective prophylaxis, considered that a choice must be made between the risk of the streptococcus on the one hand, and the staphylococcus on the other. He then stressed the following four points

1 The need for spreading the idea that the sulphonamides should not be used in the treatment of streptococcal infections

2 The superiority of continuous prophylaxis by oral penicillin or injections of benzathine penicillin.

3. The usefulness of convalescent homes for rheumatic fever patients where the child is under surveillance and knows the possible consequences of a sore throat.

4 The development of a social service for rheumatic patients comparable to the one which existed for the tuberculous.

PREVENTION OF THE FIRST ATTACK OF RHEUMATIC FEVER

by

P. Mozziconacci and J. Labesse

The problems involved in preventing a first attack of rheumatic fever differ from those involved in preventing a recurrence. The 'soil' in each differs since the risk of an attack of rheumatic fever following a streptococcal sore throat varies from less than 0.1% up to 3% in normal subjects compared with about 50% in subjects predisposed by a previous attack.

The methods of prevention at our disposal are represented essentially by the treatment of streptococcal infections since the prevention of these is rarely realisable in practise.

A. Prevention of rheumatic fever by the treatment of streptococcal infections

The fact that early and vigorous treatment of sore throats due to group A haemolytic streptococci is capable of reducing the risk of subsequent rheumatic fever has not been admitted without dispute. Finland (1947) in a review of the literature found little in its favour. Spink, Rantz, Boisvert and Coggeshall (1946) reported 6 cases of rheumatic fever in 59 soldiers with streptococcal sore throats who had been treated with penicillin, with or without sulphonamides. Weinstein, Backrach and Boyer (1949) had 12 cases (7.2%) of rheumatic fever among 167 patients with scarlet fever who had been treated with oral or parenteral penicillin. However it was not long before the effectiveness of this form of treatment became evident. It has been demonstrated in three different communities mass prevention in military camps, individual prevention in general practice and communal prevention in schools.

1. Mass Prevention

Mass prevention has been carried out on a grand scale by Rammelkamp and his colleagues who investigated many epidemics among the 8000 men at the Warren air force base, Wyoming. In the first of these studies (Wannamaker 1951) 1,178 patients who had

been given penicillin in oil with aluminium monostearate were compared with 1,162 controls. In some cases bacteriological and serological studies showed that fresh streptococcal infection had supervened. In these the late development of rheumatic fever could not be regarded as evidence of the failure of penicillin treatment of the original infection. The figures were therefore corrected by excluding all cases of rheumatic fever occurring more than 45 days after the original sore throat. (Table 1)

TABLE 1.

Incidence of rheumatic fever in patients with streptococcal pharyngitis, treated with injections of penicillin aluminium monostearate.

Treatment	Patients Treated			Controls		
	No of cases	RF definite	RF doubtful	No of cases	RF definite	RF doubtful
300,000+300,000+ 600,000 U = 1,200,000 U	516	2	1	487	20	2
300,000+300,000 U = 600,000 U	200	0	1	239	4	4
600,000 U	262	0	1	270	4	1
Total	978	2	3	996	28	7

The incidence of rheumatic fever was 28/996 = 2.8% in the controls and 2/978 = 0.2% in the treated group, a 92% reduction.

In addition the rise in antistreptolysin titre was inhibited following treatment. (Table 2)

TABLE 2.

The effect of penicillin therapy on anti streptolysin titres.

Treatment	Degree of Inhibition
300,000+300,000+600,000 U. = 1,200,000 U.	51%[1]
300,000+300,000 U. = 600,000 U	38%[1]
600,000 U	26%[1]

[1]) The percentage depression of the rise in titre in the treated group compared with the controls.

Chamovitz etal (1954) made a similar study using injections of benzathine penicillin G. 257 patients who received either 600,000 or 1,200,000 u. were compared with 109 controls (Table 3).

TABLE 3.

The incidence of rheumatic fever in patients with streptococcal pharyngitis treated with Benzathine Penicillin G.

Treatment	Patients Treated			Controls		
Benzathine Penicillin G	No of cases	RF definite	RF doubtful	No of cases	RF definite	RF doubtful
1,200,000 units	132	0	5	109	2[1])	0
600,000 units	125	0	1	—	—	—
Total	257	0	6	109	2	0

[1]) Includes 1 patient who also had acute nephritis.

There were no cases of rheumatic fever among the treated cases and 2 among the controls. As in the previous trial there was a smaller rise in ASO titre in the treated group.

The results with aureomycin (Houser et al., 1953) and with terramycin (Catanzaro et al., 1955) though also positive are not so impressive, (Table 4)

TABLE 4.

The incidence of rheumatic fever in patients with streptococcal pharyngitis treated with tetracyclines.

Treatment	No of patients	No of attacks of RF	%	% decrease
Aureomycin (Houser)	944	5	0 53%	74
Controls	972	20	2 06%	
Terramycin (Catanzaro) (2 gm. × 5 days)	506	5	0 99%	66
Controls	480	12	2.94%	

Nonetheless, these two drugs inhibited the rise in ASO titres to about the same degree as penicillin therapy (Table 5)

TABLE 5

The effect of tetracycline therapy on anti-streptolysin titres

Treatment	Number of patients	Mean rise in ASO titre	% decrease
Aureomycin	653	2 7	35 7
Controls	660	4 2	
Terramycin	489	97	49
Controls	453	187	

It may be concluded, therefore, that penicillin is the drug of choice in the prevention of first attacks of rheumatic fever by the treatment of streptococcal infection, but, where in any case this is contra-indicated, aureomycin or terramycin may be used instead.

By contrast, when used in the same way, sulphonamides are quite useless (Morris et al , 1956) Table 6).

TABLE 6.
Incidence of rheumatic fever in patients with streptococcal pharyngitis after treatment with sulphonamides.

Treatment	Number of Patients	Attacks of Rheumatic Fever		% Decrease
		Number	%	
Controls	264	11	4 2	0
Sulphonamides	261	14	5 4	

This is extremely important and instructive. Although sulphonamides have, like penicillin, a definite action on streptococcal infections (*on the fever, constitutional disturbance, local signs and* suppurative complications) they have no power to prevent subsequent rheumatic fever. They are bacteriostatic not bactericidal agents and are unable to attain the eradication of haemolytic streptococci which appears to be indispensable for the prevention of rheumatic fever.

2. Individual Prevention

The investigations so far described were simplified by the ease with which they could be undertaken in a military environment. It is desirable that prevention should be equally applicable to individuals Breese and Disney (1955) have shown that similar treatment can be carried out successfully in general practice. They treated over 2½ years 1,175 streptococcal infections in 1,075 children, with single injections of benzathine penicillin G, and have seen no cases of rheumatic fever (1 case of mild haematuria and transient albuminuria) (see Table 7). There was no control group.

TABLE 7.
Incidence of rheumatic fever in children with streptococcal infections treated with benzathine penicillin G.

Treatment	Number of Children	Number of *Streptococcal* Infections	Number of attacks of Rheumatic Fever
1 injection of 600,000 U. benzathine penicillin	1,075	1,175 (in 2½ years)	0

The difficulty in individual prevention is that of diagnosing streptococcal infections clinically. Breese and Disney (1954) have described the ways in which streptococcal infection may present and estimated the accuracy of diagnosis based on an analysis of the signs and symptoms.

TABLE 8.

Accuracy of clinical diagnosis of streptococcal pharyngitis.

Clinical Diagnosis	No. of Cases	Confirmation by Culture	Accuracy %
Negative	495	372	75
Positive	704	540	77

TABLE 9.

Frequency of Symptoms usually found in Streptococcal and Non-streptococcal Sore Throats.

Symptoms	Presence of Streptococci (%)	Absence of Streptococci (%)	Agreement
Sore throat	79	44	+2.0
Dysphagia	65	32	+2.0
Headache	51	34	+1.5
Abdominal pain	32	24	+1.3
Vomiting	33	18	+1.8
Shivering	20	14	+1.4
Cough	15	19	−1.3
Hoarseness	4	6	−1.5

The + or — signs indicated the chances for or against a haemolytic streptococcal infection.

TABLE 10.

Appearance of the throat in the 2 groups of cases.

Throat	Presence of streptococci (%)	Absence of streptococci (%)	Agreement
Normal	8	25	−3.1
Slightly inflamed	35	51	−1.5
Moderately inflamed	46	21	+2.8
Markedly inflamed	10	2	+5.0

TABLE 11.

Amount of exudate with sore throat in the 2 groups

Exudate	Presence of streptococci (%)	Absence of streptococci (%)	Agreement
None	46	73	−16
Slight	26	18	+1.4
Moderate	15	0 8	+18 8
Extensive	1	0 4	+2.5

From this study it may be concluded that:

(a) The clinical diagnosis of streptococcal sore throat can be made from various symptoms of which the most important are sore throat, dysphagia, local reddening and exudate. Less helpful are local lymph gland enlargement, otitis and leucocytosis. On these grounds a correct diagnosis can be made in 75% of cases.

(b) Because of the 25% error in clinical diagnosis a systematic search for streptococci is necessary if cases are not to be missed.

(c) The occurrence of silent streptococcal infections means that some cases will be missed in spite of all efforts. The frequency of these has been variously estimated. Massell puts it at 50% and we ourselves have seen about 50% of rheumatic relapses without sore throat.

3. "Communal" Prevention

Besides the two types of prevention already discussed there is a third applicable to groups of people and particularly groups of school children. In an interesting study organised in Youngstown, Ohio, and its environs, Bunn and Bennett, 1955, made a systematic search for throat infection supplemented by bacteriological examination of pharyngeal swabs for haemolytic streptococci. This survey at first limited to 100 children has been progressively extended to all the schools in the town and to some in neighbouring suburbs. Preliminary results were published in 1953-54, (Table 12).

TABLE 12.

Streptococcal infections in school children.

No of children followed	No. of children having throats swabbed	No of cultures made	No. of positive cultures	Treatment			Attacks of rheumatic fever
				Ad-equate	Inad-equate	None	
1,017	650	872	52	15	27	10	0

As no streptococcal epidemics were encountered during this investigation the number of positive cultures is small and the statistical value of the results is diminished accordingly. However, their importance should not be minimised The experience gained has enabled the authors to establish the conditions required for such a scheme of collective prevention, viz ·

(1) The existence of a laboratory large enough to tackle rapidly the the detection and identification of haemolytic streptococci.
(2) The existence of a social service able to ensure proper liaison between schools and the laboratory.
(3) The training of teachers who have to co-operate closely in the detection of sick children.
(4) The education of parents to accept the principles of the scheme.
(5) The establishment of good and close relations with the local practitioners who have to be convinced of the importance of the problem and instructed in the principles of treatment.
(6) The relations between school doctors, families and general practitioners must be properly defined, it being clearly understood that only detection is done at school and that treatment remains in the hands of the family doctor.

Facilities and preliminary preparations such as these should prove very effective if an epidemic of streptococcal infection occurs.

Various similar studies have been made since; by Hill (1955) and by Saslaw & Streitfell (1956), who showed that in the school population studied (Miami) 25-40% were streptococcal carriers, although only half of these had a raised ASO titre, by Russell (1956) and by Poskanzer et al (1956).

These interesting findings suggest certain observations:

a) These studies are based on the recognition of attacks of rheumatic fever using Jones' (1944, 1956) diagnostic criteria and separating the definite from the doubtful cases. The latter are often interpreted as allergic reactions, probably to penicillin, and are therefore excluded. In addition it is well recognised that a number of significant cardiac lesions occur in subjects who have never had any clear attack of rheumatic fever.

To overcome these sources of error some authors have sought to include in their series some cases in whom the diagnosis of the rheumatic state is based entirely on electro-cardiographic changes. Thus in his series Weinstein (1948) took account of these sub-clinical 'attacks' and reported rheumatic fever in 7% of 225 cases of scarlet fever. He himself pointed out the differences in interpretation which make his results so different from those of other workers (Weinstein, 1950).

b) In order to assess the value of a form of chemotherapy it is necessary to apply it in adequate dosage and the results obtained can be very varied according to the doses used.

Loge and Kilbourne (1948) bring this out clearly, their results with very frequent injections of penicillin being much better than with single daily injections. (Table 13).

TABLE 13.

Attacks of rheumatic fever following streptococcal infections treated with different dosage of penicillin

Penicillin	No of Patients	No. with Rheumatic Fever	Rise in ASO
300,000 U once daily for 7 days	47	3	64%
20,000-50,000 U 8 times a day for 4-7 days	29	0	14%
Controls	51	2	84%

Dosage and Administration of Penicillin

Rammelkamp's group (Wannamaker et al (1953) have established adequate dosages of penicillin from their studies of groups of young recruits who were followed over 11 weeks. Each group contained about 400 men with a weekly turnover of 15%.

The results obtained with oral penicillin show that eradication of streptococci is only obtained with 1 million units a day for 10 days. A smaller dose is less effective with 250,000 u/day for 10 days 35% remain carriers. A shorter course is also less effective. with 2 million u/day for 5 days 50% remain carriers.

With penicillin in oil or aluminium monstearate 4 injections of 600,000 u. are needed· 2-5% remain carriers. A single injection is useless The number of carriers remains at the original figure.

With benzathine penicillin G the results are excellent After a single injection of 1,800,000 u. there were no carriers during 40 days observation except one at 15 days With 600,000 units the results are not so good, 10% remaining carriers.

Thus the best results were obtained with benzathine penicillin [illegible]

c) Finally the stage at which treatment is begun is important though less so than has previously been thought. Brock and Siegal (1953) have shown that the inhibitory action of treatment on the formation of ASO may still be seen even after a delay of 5 days in starting. More recently Catanzaro et al (1954) have shown that eradication of haemolytic streptococci even after 9 days delay is followed by a reduced incidence of rheumatic fever.

B Prevention of Rheumatic Fever by Prevention of Streptococcal Infection

One can try to prevent attacks of rheumatic fever not only by treating streptococcal infections as they occur but by trying to prevent their occurrence. This method, the equivalent of continuous prophylaxis in rheumatic convalescent cases has only limited application. It has been used however in closed communities to prevent the spread of streptococcal infections.

The sulphonamides find a place here since, while they cannot prevent rheumatic fever once a streptococcal infection is evident, they retain their preventive value in noninfected subjects. It was by the daily administration of 0.5 gm. of sulphonamide that Coburn (1944) succeeded in checking an epidemic of streptococcal infection in the American Army in the winter of 1942–43. Watson et al (1943) checked an epidemic of scarlet fever, Hodges (1944) checked an epidemic of streptococcal sore throat, while Holbrook (1944) who obtained similar results stressed that treatment had to be continuous or frequently repeated.

This method of prevention by sulphonamides has two disadvantages. Firstly their action ceases immediately the drug is withdrawn. Hodges treated 2 groups of 5000 men in the air force with various doses of sulphonamides during a streptococcal epidemic. He found that after 2–3 days treatment with 2 gm/daily the number of cases of streptococcal sore throat or tonsillitis decreased rapidly but rose again after a relatively short time reaching the frequency found in the control group. This limited action may be related to the fact that sulphonamides are bacteriostatic not bactericidal.

Secondly, resistant strains may develop. Coburn (1949) in the American Navy found with prolonged administration of 0.5–1 gm. daily of sulphadiazine that after an initial favourable period of some months in which the number of streptococcal infections fell rapidly there was a return of a significant number of infections. Subsequent investigation showed there to be due to sulphonamide resistant organisms.

Yet a third drawback, by no means negligible is the possibility of toxic reactions to the sulphonamides such as rashes, or agranulocytosis. Several fatal cases of agranulocytosis were seen by Coburn.

Penicillin has been used in the same way to prevent streptococcal infections in healthy subjects. Bernstein et al. (1954) used a dose of 500,000 u./daily by mouth for 10 days. In their first study they treated one group for 10 days while the controls received no penicillin. After 10 days the frequency of infections in the treated group fell from 18/1000 to 5/1000, stayed down for 6 weeks and then rose again. In their second study they gave 10 days' treatment to everyone in the camp though to new recruits only in one or

two cases. The proportion in hospital fell by half in the treated group. In both these series bacteriological examination showed that streptococcus type 3 was predominant throughout the period of observation.

It is concluded that 500,000 u. oral penicillin daily for 10 days will reduce the incidence of streptococcal infection but will not completely eradicate the organism since new cases due to the same type occur.

The experience of Rammelkamp's group was similar. During a streptococcal epidemic at Warren Air Force base they gave 2,000,000 u. of penicillin a day for either 10 or 5 days to entire squadrons of the Air Force. The results were judged partly by the number of carriers found on testing random groups of 150 and partly by the numbers attending hospital for streptococcal infection.

The difference between the two groups receiving prophylaxis and the control group was very marked while treatment was being given but some weeks after it had stopped the number of carriers and of infections in the treated groups approached that in the controls. The delay is about 3 weeks so that to carry out mass prophylaxis with penicillin one can give 10 day courses repeated every 3 weeks until the end of the epidemic.

In addition this work stressed the harmlessness of penicillin so administered, less than 1% of reactions being observed and the only serious one being a case of laryngeal oedema.

Similar studies were made by Davis and Schmidt (1957) on 2,214 subjects treated with a single injection of benzathine penicillin. The protection thus obtained lasted approximately 25 days.

SUMMARY

The prevention of the first attack of rheumatic fever by the treat-
ment of strep- [illegible]

[illegible] ... sulphonamides.

The prevention of streptococcal infections themselves is only possible under certain circumstances such as epidemics in closed communities. Penicillin is the drug of choice but if this is not possible, sulphonamides.

Of the various measures discussed the most important at this

because it involves every healthy child in the community".

REFERENCES

BERNSTEIN, S H, FELDMAN, H A, HARPER, O. F, KLINGENSMITH, W. H CANTOR,

CATANZARO, F J STETSON, C. A, MORRIS, A. J, CHAMOVITZ, R., RAMMELKAMP, C H, STOLZER, B L and PERRY, W. D (1954) The role of the streptococcus in the

42 345

DAVIS, J and SCHMIDT, W C (1957) Benzathine penicillin G its effectiveness in the prevention of streptococcal infections in a heavily exposed population. New Engl J Med 256 339

FINLAND, M (1947) Use of Penicillin in infections other than bacterial endocarditis. Advances Int Med. 2 350

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, WANNAMAKER,

in treatment of

streptococcal sore throat on the streptococcal carrier state, the immunologic

response of the host, and the incidence of acute rheumatic fever Pediatrics 12 593
JONES, T. D. (1944) Diagnosis of rheumatic fever J Amer Med Ass 126 481
JONES, T. D. (1956) Criteria (modified) for guidance in the diagnosis of rheumatic fever. Circulation 13 617
LOGE, J P and KILBOURNE, E D. (1948) Penicillin treatment of streptococcal pharyngitis Ann Int Med. 29 698
MORRIS, A. J, CHAMOVITZ, R, CATANZARO, F J and RAMMELKAMP, C H (1956) *Prevention of rheumatic fever by treatment of previous streptococcal infection* Effect of sulfadiazine J Amer Med Ass 160 114
POZKANZER, D C, FELDMAN, H A, BRADENKOPF, W G, KURODA, K, DRISLANE, A and DIAMOND, E. L (1956) Epidemiology of civilian streptococcal outbreaks before and after penicillin prophylaxis Amer J Pub Health 46 1513
RUSSEL, E. L. (1956) Control of streptococcal throat infections in schools California Med 85 365
SASLAW, M S and Streitfeld, M M (1956) Group A beta hemolytic streptococci in relation to rheumatic fever Amer J Dis Child 92 550
SPINK, W W, RANTZ, L A, BOISVERT, P J and COGGESHALL, H (1946) An evaluation of sulfadiazine and penicillin in the therapy of patients with acute upper respiratory infections due to hemolytic streptococci including tonsillitis, nasopharyngitis and scarlet fever Arch Int Med. 77 260
WANNAMAKER, L. W RAMMELKAMP, C H, DENNY, F W, BRINK, W R, HOUSER, H B, HAHN, E O and DINGLE, J H (1951) Prophylaxis of acute rheumatic fever by treatment of preceding streptococcal infection with various amounts of depot penicillin Amer J Med 10 673
WANNAMAKER, L W, DENNY, F. W, PERRY, W D, RAMMELKAMP, C H, ECKARDT, G C, HOUSER, H B and HAHN, E O (1953) The effect of penicillin prophylaxis on streptococcal diseases rates and carrier state New Eng J Med 249 1
WATSON, R. F, SCHWENTKER, F F, FETHERSON, J E and ROTHBARD, S (1943) Sulfadiazine prophylaxis in an epidemic of scarlet fever J Amer Med Ass 122 730
WEINSTEIN, L, BACHRACH, L and BOYER, N H (1950) Observations on the development of rheumatic fever and glomerulonephritis in cases of scarlet fever treated with penicillin. New Eng J Med 242 1002

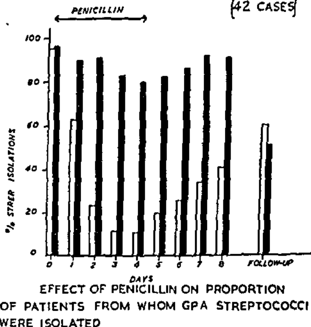
COMMUNICATION

CARRIER RATES AFTER PENICILLIN TREATMENT OF STREPTOCOCCAL SORE THROAT

by

R. CRUICKSHANK

Prof. R. Cruickshank reported some findings of his assistant, W. Brumfitt, in association with J. D. H. Slater (1951) on the treatment of acute febrile sore throat in army recruits, mostly aged 18-21 years. Among 121 consecutive and clinically indistinguishable cases of sore throat, group A streptococci were isolated



EFFECT OF PENICILLIN ON PROPORTION OF PATIENTS FROM WHOM GPA STREPTOCOCCI WERE ISOLATED

Fig 1

from 82 (66%) and not at all from 39 cases despite frequent swabbing.

Cases were allocated for treatment with penicillin on a random sampling basis and the clinical and bacteriological progress was followed daily during an 8–10 day stay in hospital and at a follow-up about 3 weeks after onset. Penicillin intramuscular injections were given twice daily for 4 days in a dose of 300,000 units procaine penicillin and 100,000 units crystalline penicillin G. The figure shows that although there was a marked reduction in the incidence of positive swabs following penicillin therapy, there was a gradual increase in the carrier rate on cessation of treatment, and at the follow-up examination the incidence of streptococcal carriers was rather higher in the treated than in the control group. These findings indicate that a course of penicillin therapy which is

clinically adequate fails to eliminate the haemolytic streptococci from the throat and thus presumably would be ineffective in preventing primary attacks of rheumatic fever following streptococcal sore throat.

DISCUSSION

J. Wickstrom agreed that streptococcal prophylaxis was justified in everyone who had had rheumatic fever but was not convinced of its value in the prevention of first attacks. Nor could he support the opinion that an upper respiratory tract disease complicated by a middle ear infection, and all upper respiratory infections in individuals living in close contact with such patients, should be considered as probable cases of streptococcal infection. In a hospital for contagious diseases at Turku, Finland, about half the children under 2 years old have otitis as a complication of an upper respiratory tract disease. Cultures obtained by tympanic paracentesis gave only a small proportion (10-25%) of streptococci. Chemotherapy in all these cases of otitis media, all cases of upper respiratory disease in their environment and all cases of upper respiratory disease in the environment of cases of scarlet fever would lead to an excessive use of antibiotics. In practice such preventive measures are hardly feasible since most slight cases are never seen by a doctor.

D. D. Rutstein regretted that at present there was no way of knowing who would be struck down by a first attack of rheumatic fever following streptococcal infection. Nor was there any known characteristic of the streptococcus or variety of antibody response which permitted a prediction of the risk of developing rheumatic fever. Until such information became available, in order to prevent first attacks of rheumatic fever it was necessary to identify and treat effectively all group A streptococcal infections, particularly when they occurred in children.

PRACTICAL APPLICATION OF AVAILABLE KNOWLEDGE IN THE PREVENTION OF RHEUMATIC FEVER

by

D. D. RUTSTEIN, BOSTON

It is now clear that it is possible to prevent relapses of rheumatic fever in known rheumatic subjects if infection with the group A haemolytic streptococcus is forestalled. Furthermore, attacks of acute rheumatic fever may be prevented in rheumatic subjects when prophylaxis fails and in normal people if all infections with

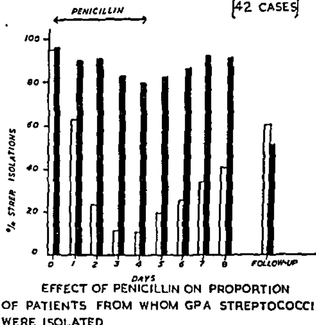


Fig. 1.

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DISCUSSION

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It is now clear that it is possible to prevent relapses of rheumatic fever in known rheumatic subjects if infection with the group A haemolytic streptococcus is forestalled. Furthermore, attacks of acute rheumatic fever may be prevented in rheumatic subjects when prophylaxis fails and in normal people if all infections with

the group A streptococcus are recognized and treated promptly so as to eradicate the microorganism.

Whenever possible, there should be an organized programme for the prevention of rheumatic fever. In some situations, when other more pressing health problems may preclude an organized programme, we should at least be concerned with protecting individual cases as they are recognized. There are certain things that can and should be done in all circumstances. It is essential that some form of efficient prophylaxis be instituted for all persons known to have rheumatic fever or chronic rheumatic heart disease. It is also necessary for us to ensure that all recognized cases of acute haemolytic streptococcal infection be given adequate treatment with penicillin.

Diagnostic Criteria

Unfortunately we do not yet have any specific diagnostic symptom, sign, or laboratory test which will establish without doubt the diagnosis of rheumatic fever. Nevertheless, the diagnosis of rheumatic fever should be made as precisely as possible before submitting patients to a prolonged period of prophylactic treatment. The most useful criteria on which to base such a diagnosis are those formulated by the late T. Duckett Jones[1] and subsequently modified. A copy of the 'Jones Criteria (Modified) for Guidance in the Diagnosis of Rheumatic Fever" is included in appendix[1]).

Recognition of Group A Streptococcal Infection

It is necessary at this time to define and clarify the recognition of beta haemolytic streptococcal infection for guidance in carrying out our programmes. For the purpose of a practical preventive programme for rheumatic fever, a haemolytic streptococcal infection is defined in terms of those clinical, epidemiological and laboratory features which are easily recognized by the practising physician. There are, of course, many streptococcal infections which may precipitate an attack of rheumatic fever and yet may be so mild or so atypical as to be practically unrecognizable. Indeed, many cannot easily be differentiated from common viral infections

[1]) Jones T. D. (1944) J Amer med. Ass. *126* 481.
(1956) Circulation *13* 617.

of the upper respiratory tract. However, a group of clinical and epidemiological syndromes exists in which there is a great probability of streptococcal infection and in which rheumatic fever may be prevented by adequate penicillin treatment The following conditions are the ones which we will want to treat rapidly and effectively with penicillin in any programme to prevent rheumatic fever.

1. Scarlet fever.

2. Pharyngitis, with or without tonsillitis, manifested by local redness, oedema, exudate and elevated temperature, and associated with enlarged tender lymph nodes at the angle of the jaw, leucocytosis or a positive throat culture

3. Complications of upper respiratory disease, or syndromes which are frequently due to the streptococcus such as otitis media, mastoiditis, and erysipelas.

4. Upper respiratory infection occurring in individuals living in households or in close contact, for example in institutions or schools, with patients with obvious streptococcal disease.

5 Symptoms at all suggestive of streptococcal disease in known rheumatic patients and in their familial household contacts.

As physicians, we have certain laboratory examinations to add to our clinical observations in differentiating streptococcal infection from other varieties of upper respiratory disease. The simplest and most readily available is probably the measurement of the white blood count It is unusual, particularly in adults, to get a marked leucocytosis in viral infections of the upper respiratory tract. On the other hand, leucocytosis does not accompany every case of streptococcal sore throat.

Cultures of the nose and throat can also be very useful in diagnosis if they are properly performed and interpreted.

It would be helpful if we were able to define in precise quantitative terms the criteria for differentiating acute streptococcal infection, the carrier state and the total absence of streptococci by the use of throat cultures. However, this is not possible because the results of a throat culture depend upon so many factors that are difficult to control

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ties. I, personally do not recommend the use of cultures except under very carefully controlled conditions. If cultures are to be used, certain procedures are recommended such as:

1. careful swabbing of both tonsils and the pharyngeal wall,
2. the use of nasal swabs in addition to throat swabs,
3. the rapid transfer to a blood agar plate before drying of the swab can occur,
4. careful streaking with a platinum loop to ensure adequate distribution of the organisms, and
5. the use of suitable blood agar media (see Wahl; p.?).

When proper facilities are available it may be useful to establish with certainty the presence of group A streptococci by isolation and further identification of haemolytic colonies.[1])

In general, although there is no precise evidence on this point, under optimal circumstances we would expect to find that throat cultures obtained from most patients with acute streptococcal sore throat will show a heavy preponderance of group A haemolytic streptococci. We might also expect that throat cultures from carriers will show comparable numbers of organisms in only a small proportion of instances.

For practical purposes, then, we might consider the recovery of large numbers of streptococci as diagnostic of streptococcal sore throat. When smaller numbers of organisms are recovered our decision as to treatment will be based on the clinical findings. The absence of streptococci in a single culture is good evidence against acute infection but does not rule out the possibility of the carrier state.

Prevention of Rheumatic Fever Recurrences

In the prevention of recurrences we are concerned with whether *or not the patient is exposed to excessive risk of infection* with the beta haemolytic streptococcus. Our technique of control will be different for the patient whose exposure is casual.

1) The methods for obtaining and interpreting throat cultures are discussed in detail in *Diagnostic Procedures and Reagents*, 4th edition. The American Public Health Association.

EXCESSIVE EXPOSURE

In the wards of hospitals or in semi-closed communities such as institutions and camps where streptococcal infection may be epidemic, control is simple and straightforward. As long as we are aware of the need for the protection of rheumatic fever patients we will act at the time of admission of the patient to the hospital or institution. This is particularly important on the medical, surgical or pediatric wards of the hospital. We will then prescribe penicillin in a form and dosage to provide relatively high and constant blood levels throughout the period of exposure. A possible schedule might be to double the dosage recommended for continuous prophylaxis. (See Mozziconnacci and Labesse in Chapter 1).

As physicians we must recognize that our job does not stop when we have written out our prescriptions. We must see that the nurses and social workers and other personnel in hospitals are educated to their responsibilities in the protection of the rheumatic fever patients in their charge They must know of the danger to the patient presented by streptococcal infection We must be sure they are informed of the desirability of seeing that the rheumatic patient avoids contact with known infection as well as of the possibility of preventing rheumatic recurrences through prophylaxis It is important that all nurses, social workers and hospital personnel are taught the typical symptoms of streptococcal infection. Then when they believe such infection to be present, they can immediately refer the patient to a physician.

It will be valuable to develop educational programs for hospital administrators Both directors of community hospital services and the administrator in charge of the individual hospital must be aware of the benefits of a preventive program to the individual patient The administrator should know about the decreases in hospital costs which result from a shortening of the hospital stay of rheumatic patients through prevention of recurrences. With the cooperation of the hospital staff the administrator should incorporate procedures into the hospital regulations for communicable disease control which will guide staff physicians and others at the time of admission of a rheumatic fever patient to the hospital It is also his responsibility to see that penicillin is available to all rheumatic patients,

regardless of economic status. If the hospital itself is unable to provide an adequate supply, the administrator will be able to explore other possible sources of funds for this purpose.

A public health agency concerned with the spread of streptococcal infection can do much to help the practising physician, particularly during epidemic periods. Its job is to warn the medical profession and hospital administrators of the presence of infection in the community and to assist in the prevention of spread of streptococcal infection to rheumatic patients.

Finally, there is a role in the preventive programme for the rheumatic patient himself and it is our job to see that he is properly prepared to play it. At the time of his first attack, or when rheumatic heart disease is first diagnosed, we must warn him of the dangers of a superimposed streptococcal infection. At the same time we can explain to him the value of penicillin and its effectiveness in protecting him under conditions of intimate exposure.

Casual Exposure:

It is more difficult to prevent streptococcal infection resulting from casual exposure under the ordinary conditions of daily life. Here we must continue prophylaxis in known rheumatic fever patients for long periods of time, even in individuals who feel perfectly well. In such circumstances, prophylaxis can be successful *only* under the following conditions.

(i) The diagnosis of rheumatic fever must be clearly established according to generally acceptable criteria. The diagnosis of rheumatic fever should never be made by exclusion. Prophylaxis must not be started unless a clearly established diagnosis exists.

(ii) As physicians, the responsibility for continued medical supervision of the patient is ours. If the patient changes frequently from physician to physician, or if we attempt to delegate our responsibility, it is unlikely that prophylaxis will be continued *successfully*.

(iii) At all times we must be convinced of the value of continuous prophylaxis, aware of its difficulties and alert to its possible dangers. We must recognize the symptoms and signs of a superimposed streptococcal infection, the supervention of a rheumatic recurrence, the development of rheumatic heart disease, and the

appearance of toxic effects or intolerance due to the drug.

(iv) We must teach the patient and his family the reasons for continuous prophylaxis and the warning signals which they must recognize as requiring our immediate attention. Unless the patient and his family really desire prophylaxis, it will not be successful. We need their cooperation and this will not be attained unless there is full understanding of the warning signals of streptococcal infection, rheumatic recurrence, and drug reactions.

(v) The public health services have much to offer which can help us ensure continuous medical supervision. Visits by public health nurses or social workers (or assistante sociale) to the patient's home, help to ensure that our recommendations are carried out. They offer added opportunity to observe and report warning signals in patients as well as the chance to encourage the patient to continue his prophylactic regimen. If it is possible to maintain a current list or register of patients with known rheumatic fever in the office of the local public health service, it will be useful to ensure that such patients are kept under continuous medical supervision and prophylaxis.

(vi) One of the problems of prophylactic drugs is their cost. Proper governmental or voluntary agencies must accept responsibility for ensuring adequate supplies of these drugs to all rheumatic fever patients regardless of economic status.

(vii) In spite of the seasonal occurrence of streptococcal infection, prophylaxis must be continued throughout the year. Recurrences of rheumatic fever do occur during the summer. Moreover, any period of interruption may make it difficult to re-institute daily continued prophylaxis. At the present time, with knowledge now available it is impossible to state exactly the desired duration of prophylaxis. A reasonable compromise would suggest that prophylaxis must be continued without interruption at least up to the age of 15, or during a period of five years following the end of the last recognizable attack of rheumatic fever, whichever period is longer. Prophylaxis should be resumed in any patient exposed to unusual risk of infection. For example, a mother with a previous history of rheumatic fever, or with rheumatic heart disease may be exposed to streptococcal infection brought into the household by her children. There are some who have recommended

continuous lifetime prophylaxis after observing late recurrences of rheumatic fever.

Which prophylactic agent to use and how to administer it are decisions which will be made on the basis of many factors. We must consider the tolerance of the patient to a monthly intramuscular injection, the economic status of the family and the availability of the drugs, and the ability of the patient or parent to accept responsibility for daily oral administration. Drug sensitivity has, of course, always to be considered. All of these factors must be weighed in the selection of the best prophylactic agent for a particular patient.

In order for all these requirements to be met we must have educational programmes which reach all those concerned in the care of the rheumatic patient. Information must be provided in medical schools, medical societies, and medical journals. Similarly, other medical personnel, particularly those visiting the patient at home, must be well informed so that they will independently encourage the patient and his family to continue prophylaxis and be able to recognize difficulties when they arise. We must reach the representatives of the community agencies, including the public health and social welfare departments, voluntary medical and social agencies and institutions such as hospitals. Finally, the patient himself must be aware of the danger of streptococcal disease and the benefits of prophylaxis.

Treatment of Superimposed Streptococcal Infection in a Rheumatic Patient

If the rheumatic patient is not under prophylaxis, or in the uncommon event of unsuccessful prophylaxis, superimposed streptococcal infection may develop. Immediate intensive treatment with large doses of penicillin for a period of time necessary for eradication of the streptococcus — 10 days — is then imperative. The great vulnerability of known rheumatic patients to recurrences after superimposed streptococcal infection is well known. Therefore, treatment should be started at the first suspicion of streptococcal disease, that is, the earliest appearance of a sore throat. We should not wait for conclusive evidence of streptococcal infection as we might in the case of normal individuals. Such treatment should be

carefully supervised in order to eradicate all evidence of streptococcal infection from the upper sulphonamide respiratory tract of the individual. Although a treatment is effective in the prevention of streptococcal infection, it should never be used for treatment except in those places where penicillin may not be available. Sulphonamides may prevent septic complications, but they will *neither prevent the subsequent development* of rheumatic fever nor eradicate the streptococci from the upper respiratory tract.

Prevention of First Attacks

The evidence pertaining to the prevention of first attacks of rheumatic fever has been reported from studies in military establishments. I know of no well-controlled published evidence documenting the prevention of first attacks of rheumatic fever in civilian population groups. Nevertheless, I still think it is possible for us to institute effective treatment with penicillin in isolated cases of streptococcal infection in the community and thus prevent rheumatic fever. *This would appear to be a simple matter,* and yet all too frequently treatment is terminated after two to four days when classical symptoms of streptococcal infection have disappeared. We must be sure to recognize the importance of prolonging treatment for ten days to ensure eradication of the streptococcus. Now that long-acting preparations for intramuscular injection of penicillin, such as dibenzyl penicillin, and compounds such as penicillin V for oral treatment are available, it should be possible to devise treatment schedules for individual patients which will give adequate blood levels for ten days. When streptococcal infection occurs in an individual in the low income group, it may *even prove economical for community agencies to provide an* adequate supply of penicillin for treatment. This is much less expensive than the prolonged care of a patient with rheumatic fever.

At this time, the prevention of first attacks of rheumatic fever consists of the above procedures supported by the streptococcus control activities of the public health agency, by methods for control of the spread of streptococcal infection in closed communities and by lay education encouraging patients who might have streptococcal infection to report to their physicians.

As yet, no effective methods of early streptococcal case-finding on a community-wide basis have been developed and much well controlled research is needed. Therefore, effective community-wide programmes for prevention of first attacks of rheumatic fever are not now possible. Preliminary uncontrolled studies have solved many of the practical problems which may be faced in the establishment of a controlled study and seem to indicate that the school health service may serve as a successful screening device. Since the prevention of first attacks of rheumatic fever will eventually depend on the recognition and early and adequate treatment of streptococcal disease, streptococcal case finding studies adapted to the special conditions of particular communities are needed.

By effective use of community and medical facilities, supported by the necessary educational programmes, we should be able to prevent most recurrences of rheumatic fever under conditions of intimate exposure to streptococcal infection, prevent many recurrences under conditions of casual exposure, and prevent occasional first attacks of rheumatic fever through effective treatment of recognized streptococcal infection.

Finally, much research is needed to give information on methods by which more streptococcal infection may be recognized and treated early so that most first attacks of rheumatic fever may be prevented.

COMMUNICATIONS

THE CONTRIBUTION OF THE SCHOOL AND STUDENT HEALTH SERVICES TO THE CAMPAIGN AGAINST RHEUMATIC FEVER

by

L. DEBBASCH

Doctors in the School Health Service are struck by the number of grave cardiac changes which they find at routine examinations and which the families know nothing about, or indeed sometimes deny. Their daily observations have led them to consider rheumatic fever as the principal cause of heart conditions and have shown the close

connection there is between respiratory infection and rheumatic fever.

Can the School Health Service contribute to the campaign against rheumatism? With the means at its disposal it cannot carry out routine swabs of the nasal and pharyngeal mucosa in children with an upper respiratory infection, but it might be possible to take swabs from the brothers and sisters of pupils absent with rheumatic fever.

The School Health Service can, however, play an important part in health education. During periodic examinations in the presence of the children's families the school doctor has plenty of scope for educating the latter. Meetings of parents and periodic teaching conferences are excellent occasions for starting a discussion on rheumatic fever and its prevention

With this in view, the School Health Service decided to carry out an enquiry into rheumatic fever in the school population of the Academy at Aix en Provence. The aim of this investigation was to assess the importance of rheumatic fever in the South-West of the country and to find out which children were affected so that they could benefit from closer medical care during their school days. At the same time the parents would be told of the need for looking for streptococcal infections and of combating them.

THE PROPHYLACTIC SERVICES OF THE PORTUGESE INSTITUTE OF RHEUMATOLOGY

by

A. Teixeira

In 1951 the Institute of Rheumatology organized the detection of rheumatic heart disease in school children in Lisbon. In 1952 the search was extended to acute and chronic rheumatism so that the gravity of the problem could be assessed and the foundations of a prophylactic service for inflammatory and degenerative rheumatism could be laid.

Through this investigation and also through the patients seen at the Institute we were able to gather together and classify several

hundreds of cases. Some had rheumatic fever with or without heart disease; others only residual cardiac involvement with no inflammatory episode; a third group was made up of suspected cases of rheumatic fever. As well as the clinical and laboratory examinations necessary for confirming the diagnosis, visits to home or place of work were made so that the medico-social problem of each patient could be assessed. A series of preventive and therapeutic measures were instituted: comprising the use of antibiotics, steroids, ear, nose and throat surgery, a system of home care as we had not enough hospital beds, and a social service which aimed at solving domestic, economic or professional problems, which might have a bearing on the aetiology of rheumatic fever.

It is obviously not easy to assess the degree of usefulness of our efforts. However, the 5 years' experience enabled us to recognise some of the peculiarities of rheumatic fever in our country and to make better use of the facilities at our disposal.

DISCUSSION

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difficulties arising from the need of treating for years apparently healthy people and economic difficulties since the most effective prophylactic was also the most expensive.

It was to be hoped that the W.H.O. Expert Committee on Rheumatic Fever would point out what measures should be adopted at international level so that the prophylaxis of rheumatic fever would not remain the [illegible] There would be grounds for [illegible]

some countries which were insufficiently equipped. The achievements of UNICEF in the treatment of tuberculous meningitis would always be remembered and they could serve as an example.

J. Sénécal was preoccupied by the following questions: Was the principle of the effectiveness of preventive treatment valid in countries where, as in certain overseas territories, there was no specialist personnel and no statistical or biological data, even though it was known that streptococcal infection was widespread? Would the considerable effort necessary for an attempt at

prophylaxis be justified? Furthermore, was there a racial difference in the response to the streptococcus?

D. D. R

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of rheumatic fever in the region concerned. As for racial differences, they had been the object of investigation but the results had been inconclusive.

M. McCarty, discussing the report published under the auspices of the American Heart Association, commented on the recommendation, which might cause some discussion, that rheumatic fever prophylaxis should be carried on indefinitely. As there were no solid facts on which a decision concerning the duration of prophylaxis could be based, it had to be

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However that might be, it was true that recurrences of rheumatic fever did occur in the adult and where heart disease was present they were a potential danger which could be serious and cause death.

These considerations formed the basis of the recommendation that in our present state of knowledge prophylaxis should be carried on indefinitely. It had been realized that exceptions should be made to the principle of continuity in adults and in special cases. However, it had proved difficult to formulate sufficiently explicit criteria to cover these exceptions. It must be left therefore to a large extent to the judgement of the

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R. C was of the opinion that when considering appropriate measures for preventing rheumatic fever more attention should be paid to the control of streptococcal infection in the community. Even though the rhythm of decline in the incidence of rheumatism seemed to be more rapid than that of streptococcal infections, it was reasonable to claim that any measure which tended to limit the dissemination of these infections would at the same time accelerate the fall in rheumatic fever. It was, therefore, proper to take a greater interest in the *dangerous spreaders* of haemolytic streptococci, e.g. children who are carriers of streptococci in the nasal fossae

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DISCUSSION

M. Sarvan considered that the prevention of rheumatic fever was a problem which many countries, especially those whose health organization was still undeveloped, could not solve by themselves. One came up against technical difficulties arising from the need of treating for years apparently healthy people and economic difficulties since the most effective prophylactic was also the most expensive.

It was to be hoped that the W.H.O. Expert Committee on Rheumatic Fever would point out what measures should be adopted at international level so that the prophylaxis of rheumatic fever would not remain the prerogative of the more advanced countries. There would be grounds for contemplating moral aid which would consist of drawing the attention of [illegible] rheumatic fever and

spurring on social insurance schemes to provide larger sums for the prophylaxis of rheumatic fever. Furthermore, economic aid would be desirable for some countries which were insufficiently equipped. The achievements of UNICEF in the treatment of tuberculous meningitis would always be remembered and they could serve as an example.

J. Sénécal was preoccupied by the following questions: Was the principle of the effectiveness of preventive treatment valid in countries where, as in certain overseas territories, there was no specialist personnel and no statistical or biological data, even though it was known that streptococcal infection was widespread? Would the considerable effort necessary for an attempt at

prophylaxis be justified? Furthermore, was there a racial difference in the response to the streptococcus?

D D Rutstein replied that if the maximum benefit was to be drawn from the funds available they should be applied to the campaign against the most widespread and most serious diseases in the country. Everything would depend on the importance of rheumatic fever in the region concerned. As for racial differences, they had been the object of investigation but the results had been inconclusive.

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observation that there was a continuous decline in the incidence of recurrences during this period of 5 years However, once this period was over, the number of recurrences did not go on dropping, but remained at the same level at least for the series of years for which there were figures The question therefore arose whether the decline was sufficient to justify the rejection of the form of insurance, which was after all inexpensive, which continuous prophylaxis represented On the other hand, since the data extended over a few years only it was not known whether the drop in the figure for recurrences would be the same in someone who had had prophylactic treatment for 5 years

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APPENDIX 1

JONES CRITERIA (MODIFIED) FOR GUIDANCE IN THE DIAGNOSIS OF RHEUMATIC FEVER [1])

Rheumatic fever is related to previous infection with Group A beta haemolytic streptococci, but the mechanism of the disease is unknown. Its boundaries are indefinite, and its differentiation from other diseases is sometimes impossible. There is no specific laboratory diagnostic test The diagnosis must therefore be arbitrary and empirical Criteria herein set forth are aimed at identifying those individuals who have had or are having an attack of rheumatic fever They make no attempt to measure rheumatic activity at any given time or to diagnose inactive rheumatic heart disease Thus, following the designation of an illness as rheumatic fever, the existence of continued activity or the presence of inactive rheumatic heart disease may be indicated by criteria different from those outlined below

Criteria are necessary in order to minimize both over-diagnosis and under-diagnosis The tendency to label as rheumatic fever a chronic febrile illness for which no obvious cause can be found is to be deplored The tragedy which may lie in the wake of the false diagnosis of rheumatic fever may be even greater than the possible harm of missed recognition in questionable cases The institution of effective prophylactic regimens requiring prolonged administration of sulfadiazine or antibiotic agents places a grave responsibility on the physician in the diagnosis of this illness

In this statement, the diagnostic features of the disease are divided, as originally proposed by Jones, into major and minor categories dependent upon their relative occurrence in rheumatic fever and in other disease syndromes from which this disease must be differentiated Thus, chorea is included among the major criteria while fever, a symptom common to many diseases, is placed in a minor category These major and minor categories have no significance beyond their diagnostic import either as to prognosis, amount of "rheumatic activity", or severity of acute illness Indeed, a severe manifestation of rheumatic fever such as rheumatic pneumonia is not included, because it is difficult to differentiate from congestive cardiac failure and because it almost always occurs in patients whose rheumatic fever is so obvious as to offer no difficulty in diagnosis

The presence of two major criteria or one major and two minor criteria indicates a high probability of the presence of rheumatic fever with one notable exception (see section on "Other manifestations", page 189) In addition to the major and minor criteria to be used in the recommended formula, other manifestations have been listed which may be used to support the diagnosis These criteria are not meant to substitute for the wisdom and judgement of the clinician They are designed only to guide him towards a diagnosis of the disease, with the suggestion that he follow carefully all questionable cases and restrict the diagnosis of rheumatic fever to illnesses which meet acceptable criteria

Major diagnostic criteria

Carditis

Carditis, as evidenced by any one of the following

Murmurs (see page 189) The presence of a significant apical systolic murmur, apical mid-diastolic murmur, or basal diastolic murmur in an individual without a history of previous rheumatic

[1]) Taken from *Circulation*, 1956, 13, 617, by kind permission of the American Heart Association.

with or without nasal discharge, or who have a running ear or a skin infection The speaker had frequently seen outbreaks of streptococcal [illegible]

[illegible]

most likely sources for the spread of infection to those around them. As for doctors, they should be persuaded of the urgent necessity of properly treating infections of this kind.

[illegible]

period when pneumococcal infections had been very frequent an era had opened which was characterized by the predominance of the streptococcus and this was tending nowadays to give way to the staphylococcus. It was not certain whether this change in the dominant organism was due to the use of antibiotics That is to say, the rules for the prophylaxis and therapy of rheumatic fever might not necessarily be valid for every country and every epoch, a certain amount of prudence was therefore indicated

However, certain general principles could be considered as established: [illegible]

4) the restricted use of sulphonamides which were only to be considered in the prophylaxis of recurrences.

Hospitals and convalescent homes should play the part of health education centres for patients and their families by emphasizing the risks of a new streptococcal infection Hence the importance of detecting in the schools cases of sore throat, otitis, arthritis and nephritis.

A pilot station was going to be organized in the laboratories of the International Children's Centre whose task would be the study of the measures necessary to check the spread of streptococcal infection in certain communities and schools The views of those taking part in the seminar would be invaluable in setting up the working plan for this station and in the later assessment of the work which it might accomplish This would not be easy as rheumatic fever was showing a spontaneous tendency to dimished incidence.

Previous history of rheumatic fever or the presence of inactive rheumatic heart disease

The existence of either of these may be used as a minor criterion to aid in deciding the rheumatic nature of the illness in question For this use, the previous history must be documented by the same objective criteria as are set forth in this statement or by the presence of inactive rheumatic heart disease

Other manifestations

These include systemic manifestations such as loss of weight, easy fatigability, elevated sleeping pulse rate (tachycardia out of proportion to fever), malaise, sweating, pallor or anaemia, and local manifestations such as epistaxis, erythema nodosum, precordial pain, abdominal pain, headache, and vomiting These, as well as a family history of rheumatic fever, provide additional evidence of the presence of rheumatic fever but are not to be included as diagnostic criteria

There are combinations of these diagnostic criteria which occur in the presence of other illnesses which must be ruled out before a definitive diagnosis is made One combination in particular —polyarthritis, fever, and elevated sedimentation rate—is the weakest of all combinations of major and minor criteria Diseases to be ruled out include rheumatoid arthritis, gonococcal arthritis, lupus erythematosus disseminatus, subacute bacterial endocarditis, nonspecific pericarditis with effusion, leukaemia, sickle-cell anaemia, serum sickness (including manifestations of penicillin sensitivity), tuberculosis, poliomyelitis, undulant fever, and septicaemias, particularly meningococcaemia

Murmurs indicating carditis

Significant apical systolic murmur

A significant apical systolic murmur is long, filling most of the systole, is heard best at the apex, is as well transmitted toward the axilla as over the precordium, and does not change with position or respiration It must be differentiated from an innocent (functional) murmur which is frequently found in normal people This innocent murmur is systolic, occasionally harsh, is heard best along the left sternal border and usually changes with position and respiration Borderline systolic murmurs, intermediate in location and nature, occur and should be carefully watched Questionable murmurs which are intermittently present or which, after a period of observation, cannot be clearly classified as significant are rarely of any import

Apical mid-diastolic murmur

A significant organic apical systolic murmur is frequently accompanied by a low-pitched, short, mid-diastolic murmur which is sharply localized to the chest wall over the apex of the heart and is often heard best with a patient in the left lateral position with the breath held in expiration This murmur, rarely present in the absence of an apical systolic murmur, confirms the significant nature of the latter It must be differentiated from the long, low-pitched, crescendo apical pre-systolic murmur followed by an accentuated mitral first sound, which is indicative of mitral stenosis but not of acute carditis

Basal diastolic murmur

The development of a basal diastolic murmur of aortic insufficiency is also indicative of carditis It is an early, short diminuendo murmur usually heard only, or heard best, along the left sternal border in deep expiration It has great diagnostic value, even though it may be difficult to hear and may be present only intermittently

fever or in whom there is good reason to believe there was no pre-existing rheumatic heart disease, or a change in the character of any of these murmurs under observation in an individual with a history of rheumatic fever or rheumatic heart disease

Increasing cardiac enlargement Obviously increasing cardiac enlargement by X-ray.

Pericarditis Pericarditis manifested by a friction rub, pericardial effusion, or definite electrocardiographic evidence.

Congestive failure. Congestive heart failure (in a child or young adult under 25), in the absence of other causes

Polyarthritis

Polyarthritis tends to be migratory and is manifested by pain and limitation of active motion, or by tenderness, heat, redness or swelling of two or more joints Arthralgia alone without objective evidence of joint involvement is not a major manifestation

Chorea

This must be differentiated from habit spasm, athetosis, and cerebellar ataxia Movements must be characteristic, involuntary and of moderate severity if chorea is to be used as a major manifestation

Subcutaneous nodules

These are shot-like, hard bodies seen or felt over the extensor surface of certain joints, particularly elbows, knees and wrists, in the occipital region, or over the spinous processes of the thoracic and lumbar vertebrae

Erythema marginatum

This recurrent, pink, characteristic rash of rheumatic fever, in which the colour gradually fades away from its sharp scalloped edge, is found mainly over the trunk, sometimes on the extremities, but not on the face It is transient, is brought out by heat, and migrates from place to place

Minor diagnostic criteria

Fever

A significant rise in temperature is a common symptom but, because it occurs in so many illnesses, it has little differential diagnostic value In order to be included, the elevation in temperature must clearly exceed the normal diurnal fluctuation, in which there is great individual variation.

Arthralgia

Pain clearly located without objective findings is only a minor criterion for diagnosis The pain must be in the joint, not in the muscles or other periarticular tissues, and must be distinguished from the nocturnal pain in the extremities occurring in normal children Arthralgia must not be used as a minor criterion when polyarthritis is included as a major criterion

Prolonged P-R interval in the electrocardiogram

Prolongation of the P-R interval may be non-specific, it is considered a minor criterion and is not diagnostic of carditis It cannot be used if carditis is already included as a major manifestation

Increased erythrocyte sedimentation rate, presence of C-reactive protein, or leukocytosis

Elevation in one or more of these non-specific tests may be considered as a single minor criterion *Particularly to be* deplored is the tendency to use any of these tests as a major criterion or as diagnostic of rheumatic fever There are many other non-specific tests, but these three are most commonly used

Evidence of preceding beta haemolytic streptococcal infection

This must be documented by: (1) a history of scarlet fever or by a typical clinical picture of other streptococcal infection preceding the onset of rheumatic fever by one week to one month, the nature of the infection being confirmed by a history of immediate contact with other individuals having typical streptococcal infection or by positive culture of the nose or throat in which beta haemolytic streptococcus predominates; or (2) an elevated or rising antistreptolysin-O titre

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APPENDIX 2

LIST OF PARTICIPANTS

Chairman

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Rapporteurs

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P. Mozziconacci, Research Unit on Rheumatic Diseases, International Children's Centre, Paris
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Participants

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G Attal	(Paris)
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A. Bertoye	(Lyons)
Pr Bogdanowicz	(Warsaw)
A Breton	(Lille)
A Bukiet	(Paris)
B F Carey	(New-York)
R. Caramanian	(Paris)
M Caravanho	(Paris)
P Carlo	(Philadelphia)
H. Carlson	(London)
M Carraz	(Lyons)
R. Carron	(Lyons
H. van Cauwenberghe	(Liège)
J Chaptal	(Montpellier)
P Chassagne	(Paris)
J Chevallier	(Paris)
F Choffe	(Paris)
E T. Conybeard	(London)
F Coste	(Paris)
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R. Cruickshank	(London)
Ch Curd	(Suva)
Y. Dagonet	(La Roche-Guyon)
G. Daguet	(Paris)
L. Debbash	(Marseille)
J Delafresnaye	(Paris)
P Denys	(Louvain)
G. Desbuquois	(Tours)
R. Dubois	(Brussels)
Mme Dupuy-Joie	(Paris)
V. Faber	(Copenhagen)
J Fasquelle	(Paris)
D Fettich	(Ljubljana)
M Gauthier	(Paris)
Cl. Gerbeaux	(Paris)
D German	(Lyons)
Ch. Gernez-Rieux	(Lille)
W Goslings	(Leiden)
Mlle Hartman	(Paris)
W Hijmans	(Leiden)
D. Hioco	(Paris)
C. Hooft	(Gand)
Ph. Isorni	(Versailles)
T. Jersild	(Copenhagen)
J-C. Job	(Paris)
R. Joseph	(Paris)
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M. Mayer	(Dublin)
B Meyer	(Paris)
L Cayolla da Motta	(Lisbon)
N Nazareff Ribeire	(Paris)
N Neimann	(Nancy)
J Nouaille	(Paris)
R. Pakula	(Warsaw)
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S Rahman	(Paris)
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M. Ribiere	(Paris)
M. Sarvan	(Sarajevo)
W. Schmidt	(Paris)
O Schweisguth	(Paris)
J Senecal	(Dakar)
Mme Slomska	(Warsaw)
G Sotgiu	(Bologne)
Mme. Stolova	(Prague)
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S. Williams	(Melbourne)

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INDEX